Translation of priority document

APPLICATION FOR PATENT

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TITLE OF INVENTION

NOVEL N-HYDROXY THIOUREA, UREA AND AMIDE COMPOUNDS AND THE PHARMAC EUTICAL COMPOSITIONS CONTAINING THE SAME

The above application is filed in accordance with Article 42 of th e Korean Patent Law.

Date: October 17, 2002
Agent: Patent attorney SHIN, Dong-In(seal)

Request for the Examination is filed herewith in accordance with A rticle 60 of the Korean Patent Law.

Date: October 17, 2002
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To the commissioner of
The Korean Industrial Property Office

DECLARATION

I, the below named translator, hereby declare:

(1) That my name, mailing address and citizenship are as stated below:

(2) That I am knowledgeable in the English and Korean languages and Korean Patent Application No. 2002-0063414 were filed on October 17, 2002; and

(3) That I have translated said Korean Patent Application No. 2002-0063414 into English, which English text is attached hereto, and believe that said translation is a true and complete translation of the afore-mentioned Korean patent application.

March 18, 2005

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NOVEL N-HYDROXY THIOUREA, UREA AND AMIDE COMPOUNDS AND THE PHARMACEUTICAL COMPOSITIONS COMPRISING THE SAME

Technical Field

The present invention relates to novel n-hydroxythiourea, urea and amide compounds as a potent vanilloid receptor antagonist and the pharmaceutical compositions comprising the same.

Background Art

Capsaicin (8-methyl-N-vanillyl-6-nonenamides; CAP) is a main pungent component in hot pepper. Hot pepper has been used, for a long time, not only as a spice but also as a traditional medicine in the treatment of gastric disorders and when applied locally, for the relief of pain and inflammation (Szallasi and Blumberg, *Pharm. Rev.*, 51, pp159-211, 1999). CAP has wide spectra of biological actions, and not only exhibits effects on the cardiovascular and respiratory systems but also induces pain and irritancy on local application. However, CAP after such induction of pain induces desensitization to both CAP itself and other noxious stimuli to make the pain stopped. Based on those properties, CAP and its analogues such as olvanil, nuvanil, DA-5018, SDZ-249482, resiniferatoxin have been either used as an analgesic agent, therapeutic agent for incontinentia urinae or skin disorder and under development (Wriggleworth and Walpore, *Drugs of the Future*, 23, pp531-538, 1998).

Transmissions for the mechanical, thermal and chemical noxious stimuli mainly occurred by primary afferent nerve fibers of fine unmyelinated nerve (C-fiber) and thin myelinated nerve (A-fiber), and main reaction site of CAP and its analogues called as vanilloid is present at the nerve fiber transmitting the noxious stimuli. CAP acts on the receptor existing on those neurons to induce potent irritation caused by potent inflow of mono-valent and di-valent

cations such as calcium or sodium ion, and then exhibits potent analgesic effect by blocking the nervous function (Wood et al.; *J. Neurosci.*, 8, pp3208-3220, 1988).

Vanilloid receptor-1 (VR-1) has been recently cloned and its existence becomes clear (Caterina et al.; *Nature*, 389, pp816-824, 1997). It has been clarified that this receptor transmits not only the stimuli by CAP analogues (vanilloid) but also various noxious stimuli such as proton, thermal stimuli etc. (Tominaga et al.; *Neuron*, 21, pp513-543, 1998). Based on this, it is considered that VR functions as an integrative modulator against various noxious stimuli and carries out critical role in the transmission of pain and noxious stimuli. Recently, knock-out mouse in which gene encoding for vanilloid receptor was deleted, was prepared (Caterinal et al.; *Science*, 288, pp306-313, 2000: Davis et al.; *Nature*, 405, pp183-187, 2000). Compared with normal mice, the knock-out mouse was found out to exhibit significantly reduced response to thermal stimuli and thermal pain, while no difference in the respect of general behavior, of which result reconfirms the importance of VR in the transmission of noxious sensor. However, other endogenous ligand excepting proton, not exogenous ligand such as CAP, has been not known to be actually involved in transmission of noxious stimuli at VR till now.

In accordance with the study of present inventors, it has been confirmed that leukotrienes metabolites such as 12-hydroperoxyeicosatetraenoic acids (Hwang et al., *Proc. Natl. Acad. Sci. U. S. A.*, 11, pp6155-6160, 2000) and arachidonic acid such as anandamide (Zygmunt et al., *Trends in Pharmacol. Sci.*, 21, pp43-44, 2000) act as an endogenous ligand on vanilloid receptor but proton is regarded as a receptor-activating cofactor rather than a direct ligand.

Capsaicin-reactive sensory neuron and the vanilloid receptor existing therein are distributed to the whole body and act on the expression of inflammation besides basic function such as the transmission of pain and noxious signal, which is related to asthma, anaphylactic urinary bladder hypersensitiveness, irritable bowel syndrome and the etiology of skin disease.

Nowadays, the role of afferent sensory nerve showing reactivity on capsaicin in gastrointestinal damage has been highlighted and it causes to release peripheral neuronal peptide such as calcitonin gene-related peptide in order to improve the micro blood flow in as well as to show the contradict property of the protecting gastric injury and inducing gastric injury by the stimulation of sympathetic nervous system (Ren et al., *Dig. Dis. Sci.*, 45, pp830-836, 2000). Vanilloid receptor antagonist blocking vanilloid receptor, can be used for the purpose of preventing or treating above-mentioned various diseases.

Through binding endogenous pain-inducing molecules such as anandamide or HETE to receptor, the cations are influxed into a neuron to transmit the pain.

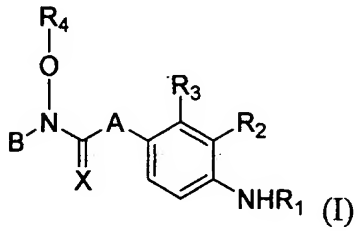
Antagonists competently inhibit the pain-inducing molecules from binding to receptor so that they can be used as analgesics with no side effect, occurring in the treatment by using agonist thereof such as initial irritancy.

Capsazepine, capsazocaine and ruthenium complex have been known as vanilloid receptor antagonists. The antagonistic effect of capsazocaine has not been reported at the level of receptor and ruthenium red has been known as a noncompetitive antagonist. Therefore, capsazepine has been reported as only one among true receptor competitive antagonists, which been paid attention to for the development of analgesics

The present inventors have made extensive researches to discover novel analgesic agents based on the above studies and finally completed the invention by the synthesis of N-(4-sulfonylamido)benzyl thiourea derivative and (4-sulfonylamido)phenyl acetamide derivative compound having excellent solubility and analgesic activity from the thiourea compound disclosed in the Korea patent application No. 2001-50092 and No. 2001-50093, the disclosure of which cited documents are incorporated herein by reference.

Disclosure of the invention

Thus, the present invention provides novel compounds represented by the following general formula (I), the pharmaceutically acceptable salt or the isomer thereof:

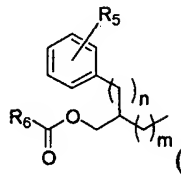


(I)

wherein

X is an oxygen or sulfur atom;

A is an aminomethylene or methylene group;

B is a 4-*tert*-butylbenzyl, a 3,4-dimethylphenylpropyl, an oleyl or 

(I-1) group wherein m is integer of 0 or 1 and n is 1 or 2;

R_1 is a halogen-substituted or unsubstituted lower alkylsulfone having 1 to 5 carbon atoms, arylsulfone or a lower alkylcarbonyl group having 1 to 5 carbon atoms;

R_2 is a hydrogen atom, a methoxy group or halogen atom;

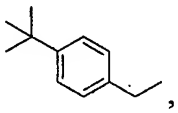
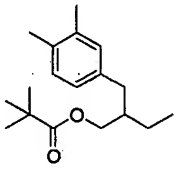
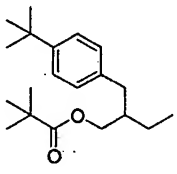
R_3 is a hydrogen atom, a methoxy group or halogen atom;

R_4 is a hydrogen atom or a lower alkyl group having 1 to 5 carbon atoms;

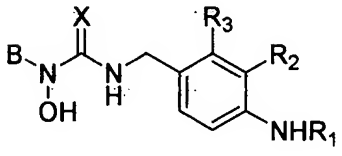
R_5 is a hydrogen atom or a lower alkyl group having 1 to 5 carbon atoms;

R_6 is a lower alkyl group having 1 to 5 carbon atoms or a phenyl group.

It is another object of the present invention to provide the pharmaceutical composition comprising an efficient amount of the compound represented by general formula (I) or the pharmaceutically acceptable salt thereof as an active ingredient in amount effective to alleviate or treat pain diseases or inflammatory diseases together with pharmaceutically acceptable carriers or diluents.

The group having general formula (I) wherein R_1 is a methylsulfonyl group; R_2 is a hydrogen atom, a methoxyl group or a halogen atom; R_3 is a hydrogen atom or a halogen atom; R_4 is a hydrogen atom; X is an oxygen atom or a sulfur atom; A is an aminomethylene group; B is  ,  or  group are preferable.

Accordingly, the present invention also provides the compounds represented by following general formula (III), the pharmaceutically acceptable salt or the isomer thereof:


(III)

wherein the definitions of X, B, R_1, R_2 and R_3 substituents are same as those of general formula (I).

In preferred embodiment, the most preferred compound is one selected from the group consisting of;

N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[4-(methylsulfonylamino)benzyl]thiourea,

N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[3-methoxy-4-(methylsulfonylamino) benzyl]thiourea,

N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[3-fluoro-4-(methylsulfonylamino)benzyl] thiourea,

N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[3-chloro-4-(methylsulfonylamino)benzyl] thiourea,

N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[4-(methylsulfonylamino)-3-nitrobenzyl] thiourea,

N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[2-fluoro-4-(methylsulfonylamino)benzyl] thiourea,

N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[2-chloro-4-(methylsulfonylamino)benzyl] thiourea,

N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[4-(methylsulfonylamino)benzyl] thiourea,

N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[3-methoxy-4-(methylsulfonylamino)benzyl] thiourea,

N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[3-fluoro-4-(methylsulfonylamino)benzyl] thiourea,

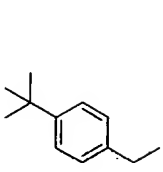
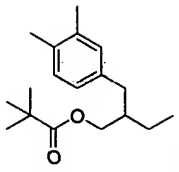
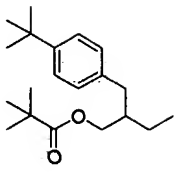
N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[2-fluoro-4-(methylsulfonylamino)benzyl] thiourea,

N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[2-chloro-4-(methylsulfonylamino)benzyl] thiourea,

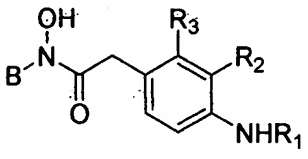
N-[2-(4-*tert*-butylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[4-(methylsulfonylamino)benzyl] thiourea,

N-[2-(4-*tert*-butylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[3-fluoro-4-(methylsulfonylamino)benzyl] thiourea.

The group having general formula (I), wherein R_1 is a methylsulfonyl group; R_2 is a hydrogen atom, a methoxyl group or a halogen atom; R_3 is a hydrogen atom or a halogen atom; R_4 is a hydrogen atom; X is an oxygen atom; Y is a nitrogen atom; A is an methylene group; B is

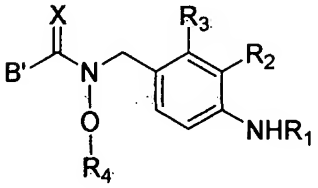
 ,  or  group are preferable.

Accordingly, present invention also provides the compound represented by general formula (IV), the pharmaceutically acceptable salt or the isomer thereof:

 (IV)

wherein the definitions of B, R_1, R_2 and R_3 substituents are same as those of general formula (I). In preferred embodiment, the most preferred compound comprises N-(4-*tert*-butylbenzyl)-N-hydroxy-[4-(methylsulfonylamino)phenyl] acetamide.

Also, it is another object of the present invention to provide compound represented by general formula (II) or the pharmaceutically acceptable salt or the isomer thereof.

 (II)

wherein

X is an oxygen or sulfur atom;

B' is an aforementioned B or a secondary amine substituted with B;

R_1 is a halogen-substituted or unsubstituted lower alkylsulfone having 1 to 5 carbon atoms, arylsulfonyl group or lower alkylcarbonyl group having 1 to 5 carbon atoms;

R_2 is a hydrogen atom, a methoxy group or halogen atom;

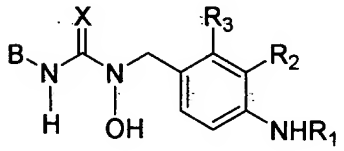
R_3 is a hydrogen atom, a methoxy group or halogen atom;

R_4 is a hydrogen atom or a lower alkyl group having 1 to 5 carbon atoms.

It is another object of the present invention to provide the pharmaceutical composition comprising the compound having general formula (II) or the pharmaceutically acceptable salt thereof as an active ingredient in amount effective to alleviate or treat pain diseases or inflammatory diseases together with pharmaceutically acceptable carrier or diluents.

The group having general formula (II) wherein B' is a secondary amine group substituted with aforementioned B; R_1 is a methylsulfonyl group; R_2 is a hydrogen atom or a halogen atom; R_3 is a hydrogen atom; R_4 is a hydrogen atom; X is an oxygen atom or a sulfur atom are preferable as the third group.

Accordingly, present invention also provides the compound represented by general formula (V), the pharmaceutically acceptable salt or the isomer thereof:



(V)

wherein the definitions of X, B, R_1, R_2 and R_3 substituents are same as those of general formula (I).

In preferred embodiment, the most preferred compound is one selected from the group consisting of

N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[4-(methylsulfonylamino)benzyl]thiourea,

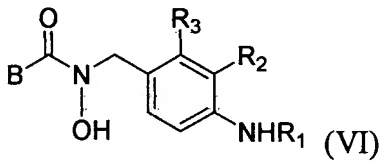
N-[2-(3,4-dimethylbenzyl)-3(pivaloyloxy)propyl]-N-hydroxy-N-[4-(methylsulfonyl amino)benzyl]thiourea,

N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[4-(methylsulfonylamino)benzyl]urea,

N-[2-(3,4-dimethylbenzyl)-3(pivaloyloxy)propyl]-N-hydroxy-N-[3-fluoro-4-(methylsulfonylamino)benzyl]thiourea.

The group having general formula (II) wherein B' is an aforementioned B; R_1 is a methylsulfonyl group; R_2 is a hydrogen atom, a methoxyl group or a halogen atom; R_3 is a hydrogen atom or a halogen atom; R_4 is a hydrogen atom; X is an oxygen atom are preferable as the fourth group.

The present invention also provides the compound represented by general formula (VI), the pharmaceutically acceptable salt or the isomer thereof:



(VI)

wherein the definitions of B, R_1, R_2 and R_3 substituents are same as those of general formula (I).

The preferred compound comprises N-hydroxy-N-[4-(methylsulfonylamino)benzyl]-2-(4-*tert*-butylphenyl)acetamide.

The inventive compounds represented by general formula (I) or (II) can be transformed into their pharmaceutically acceptable salt and solvates by the conventional method well known in the art. For the salts, acid-addition salt thereof formed by a pharmaceutically acceptable free acid thereof is useful and can be prepared by the conventional method. For example, after dissolving the compound in the excess amount of acid solution, the salts are precipitated by the water-miscible organic solvent such as methanol, ethanol, acetone or acetonitrile to prepare acid addition salt thereof and further the mixture of equivalent amount of compound and diluted acid with water or alcohol such as glycol monomethylether, can be heated and subsequently dried by evaporation or filtrated under reduced pressure to obtain dried salt form thereof.

As a free acid of above-described method, organic acid or inorganic acid can be used. For example, organic acid such as methansulfonic acid, *p*-toluensulfonic acid, acetic acid,

trifluoroacetic acid, citric acid, maleic acid, succinic acid, oxalic acid, benzoic acid, lactic acid, glycolic acid, gluconic acid, galacturonic acid, glutamic acid, glutaric acid, glucuronic acid, aspartic acid, ascorbic acid, carbonylic acid, vanillic acid, hydroiodic acid and the like, and inorganic acid such as hydrochloric acid, phosphoric acid, sulfuric acid, nitric acid, tartaric acid and the like can be used herein.

Further, the pharmaceutically acceptable metal salt form of inventive compounds may be prepared by using base. The alkali metal or alkali-earth metal salt thereof can be prepared by the conventional method, for example, after dissolving the compound in the excess amount of alkali metal hydroxide or alkali-earth metal hydroxide solution, the insoluble salts are filtered and remaining filtrate is subjected to evaporation and drying to obtain the metal salt thereof. As a metal salt of the present invention, sodium, potassium or calcium salt are pharmaceutically suitable and the corresponding silver salt can be prepared by reacting alkali metal salt or alkali-earth metal salt with suitable silver salt such as silver nitrate.

The pharmaceutically acceptable salt of the compound represented by general formula (I) or (II) comprise all the acidic or basic salt which may be present at the compounds, if it does not indicated specifically herein. For example, the pharmaceutically acceptable salt of the present invention comprise the salt of hydroxyl group such as the sodium, calcium and potassium salt thereof; the salt of amino group such as the hydrogen bromide salt, sulfuric acid salt, hydrogen sulfuric acid salt, phosphate salt, hydrogen phosphate salt, dihydrophosphate salt, acetate salt, succinate salt, citrate salt, tartarate salt, lactate salt, mandelate salt, methanesulfonate(mesylate) salt and *p*-toluenesulfonate (tosylate) salt etc, which can be prepared by the conventional method well known in the art.

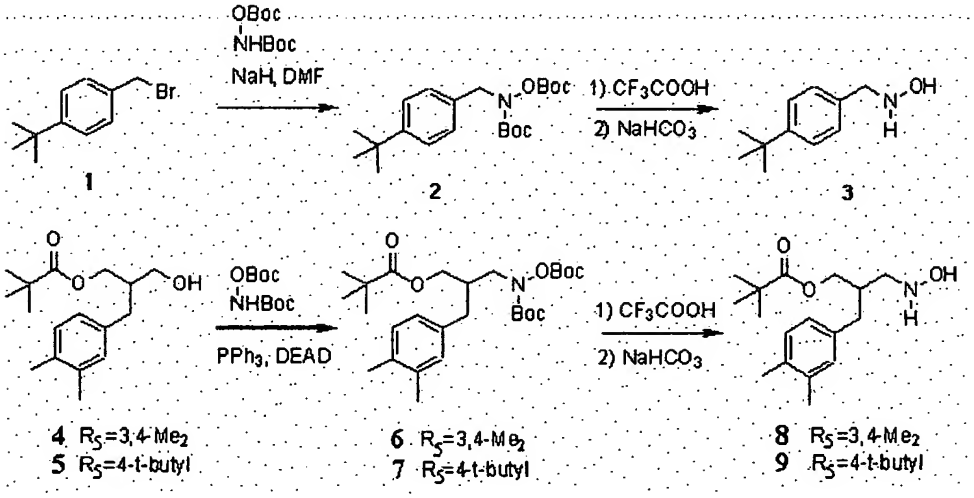
There may exist in the form of optically different diastereomers since the compounds represented by general formula (I) or (II) have unsymmetrical centers, accordingly, the

compounds of the present invention comprise all the optically active isomers, R or S stereoisomers and the mixtures thereof. Present invention also comprises all the uses of racemic mixture, more than one optically active isomer or the mixtures thereof as well as all the preparation or isolation method of the diastereomer well known in the art.

The compounds of the invention of formula (I) or (II) may be chemically synthesized by the methods which will be explained by following reaction schemes hereinafter, which are merely exemplary and in no way limit the invention. The reaction schemes show the steps for preparing the representative compounds of the present invention, and the other compounds also may be produced by following the steps with appropriate modifications of reagents and starting materials, which are envisaged by those skilled in the art.

GENERAL SYNTHETIC PROCEDURES

Scheme 1

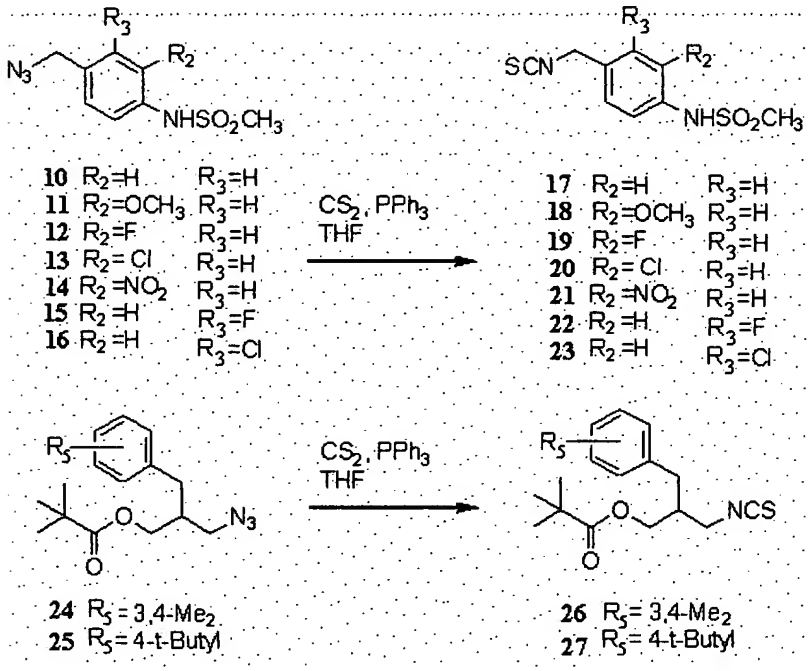


As depicted in above Scheme 1, 4-*tert*-buthylbenzyl bromide 1 is reacted with *tert*-butyl-N-(*tert*-butoxycarbonyloxy)carbamate under the basic condition to synthesize compound 2, and

then Boc(*tert*-butoxycarbonyl) group of compound 2 is removed under the acidic condition to synthesize hydroxylamine compound 3.

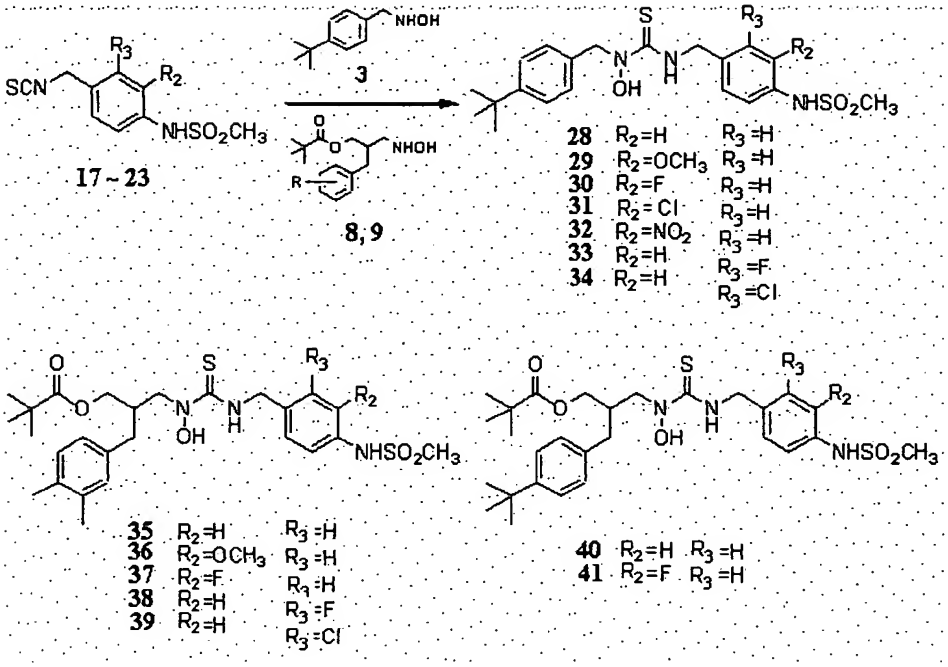
Compound 4 or 5 is condensed with *tert*-butyl-N-(*tert*-butoxycarbonyloxy) carbamate according to Mitsunobu reaction to synthesize compound 6 or 7 and subsequently hydroxylamine compound 8 and 9 are synthesized by removing deprotection group of compound 6 or 7.

Scheme 2



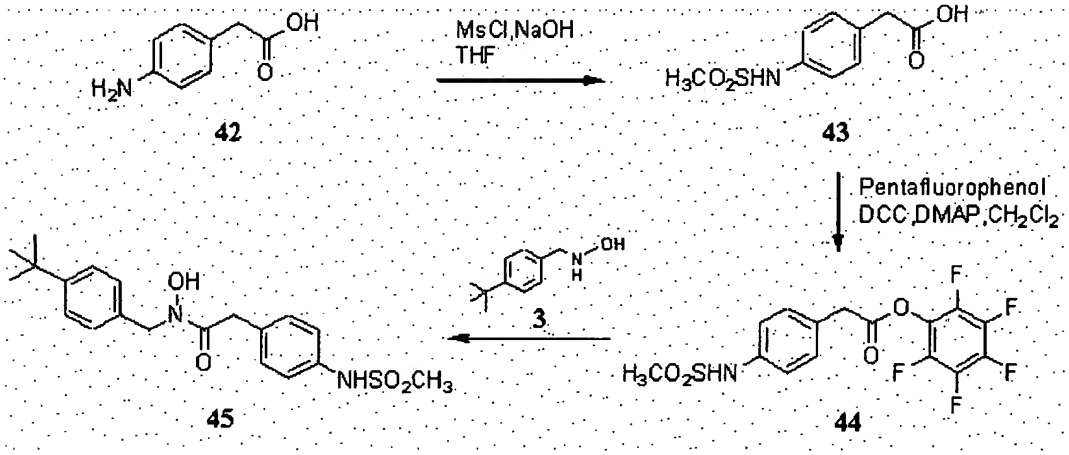
As depicted in the above Scheme 2, the azide compounds 10 to 16 and 24, 25 disclosed in Korea patent application Nos. 2001-50092 and 2001-50093 are reacted with PPh_3 and CS_2 to produce isothiocyanate compound 17 to 23, 26 and 27.

Scheme 3



As depicted in the above Scheme 3, the isothiocyanate compound 17 to 23 of scheme 2 is condensed with hydroxylamine 3 and compound 8 or 9 to synthesize N-hydroxy thiourea compounds 28 to 41 having methylsulfonylaminobenzyl group.

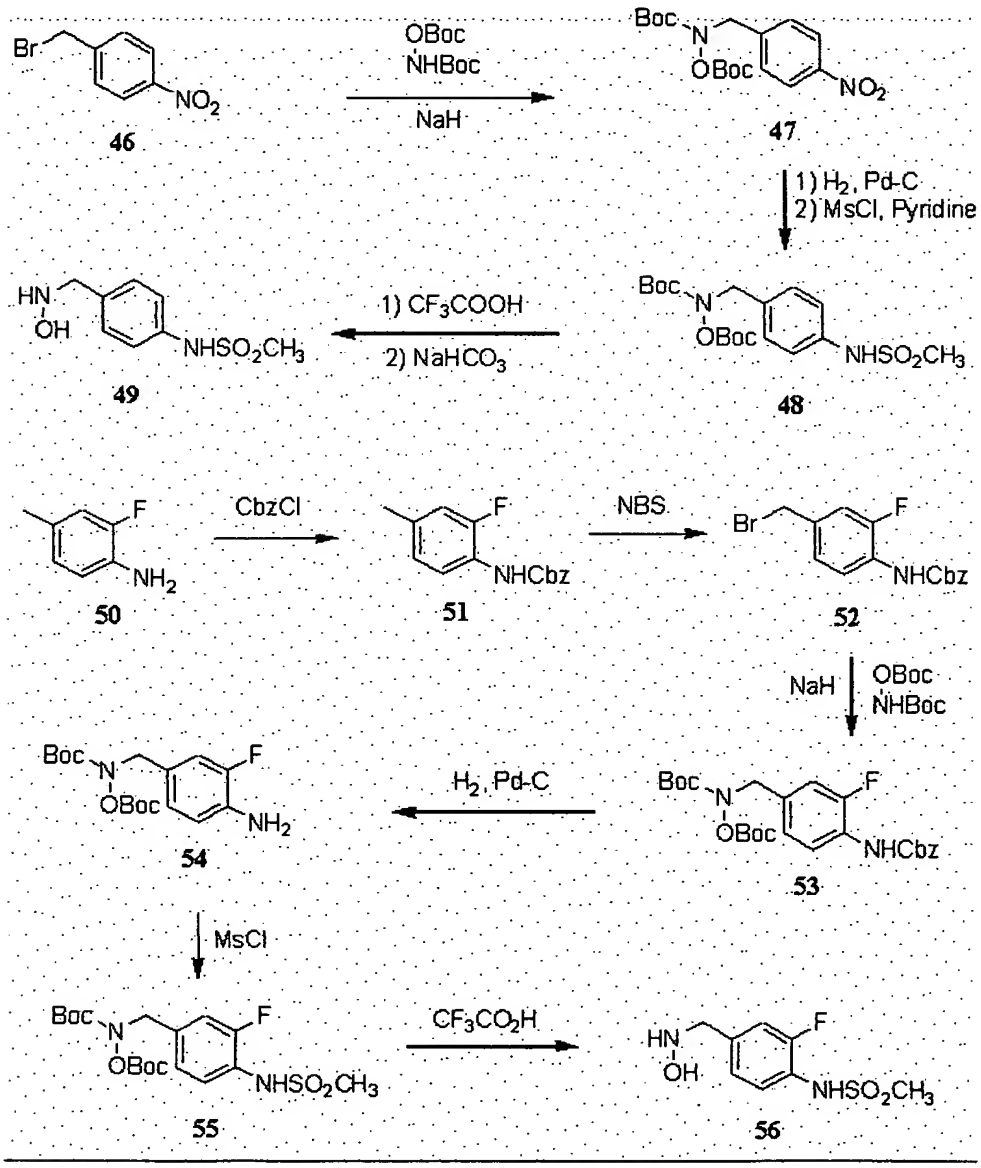
Scheme 4



As shown in the above Scheme 4, 4-aminophenylacetic acid 42 is used as a starting material, and its amine group is mesylated and its acid moiety is converted to pentafluorophenylester to produce compound 44.

The compound 44 is condensed with hydroxylamine 3 to synthesize N-hydroxy amide compound 45 having 4-methylsulfonylaminobenzyl group.

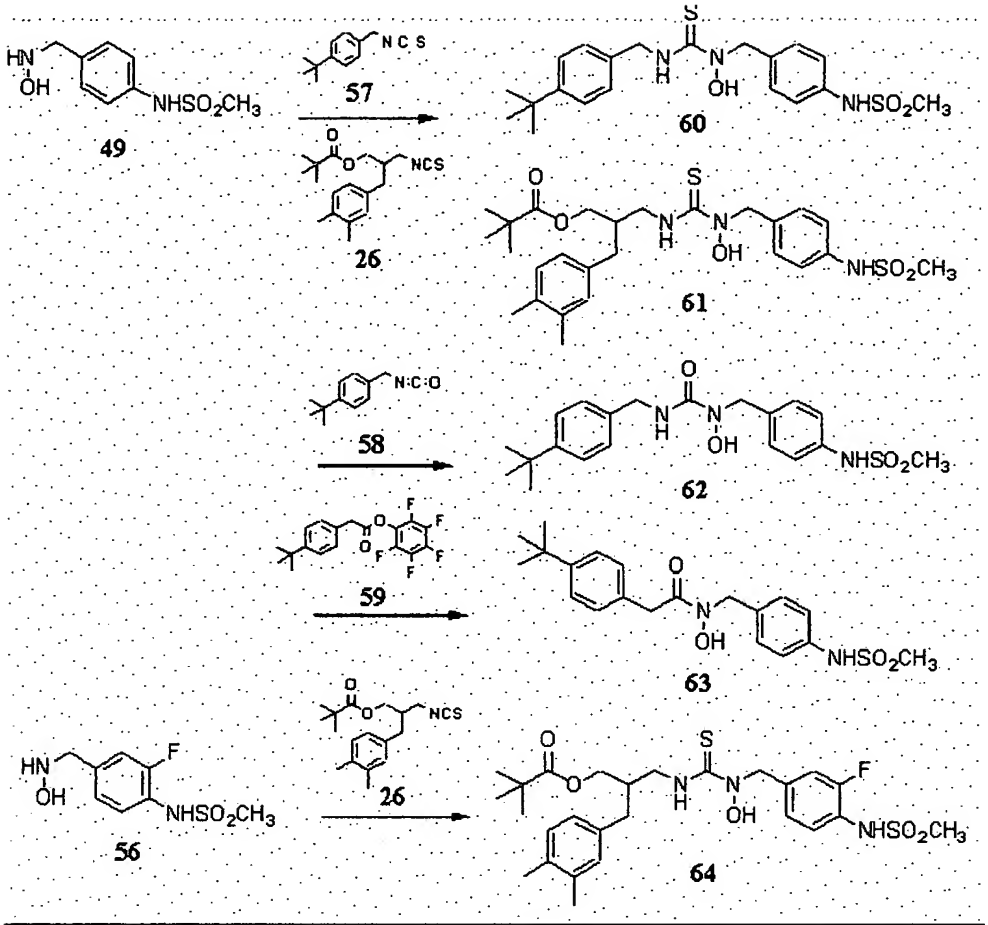
Scheme 5



As shown in Scheme 5, 4-nitrobenzyl bromide 46 as a starting material is reacted with *tert*-butyl-N-(*tert*-butoxylcarbonyloxy)carbamate under the basic condition to synthesize compound 47 and after reducing the nitro group thereof, the mesylation is performed to synthesize the compound 48. And then the Boc protecting group is removed under acidic condition with sodium bicarbonate to produce hydroxylamine compound 49.

In the synthesis of 3-fluoro derivative of compound 49, the amine group of 2-fluoro-4-methylaniline 50 as a starting material is protected with carbobenzoxy group (Cbz) and the methyl group thereof is brominated to synthesize compound 52. The compound 52 is reacted with *tert*-butyl-N-(*tert*-butoxycarbonyloxy)carbamate under basic condition to produce compound 53. After Cbz group of compound 53 is removed under catalytically reduction condition to produce compound 54 and the methanesulfone group thereof is condensed to synthesize compound 55. Finally, the Boc group is removed under acidic condition to obtain hydroxylamine compound 56.

Scheme 6



As shown in Scheme 6, hydroxylamine compound 49 is reacted with isothiocyanate 57 or compound 26 to synthesize N-hydroxythiourea compound 60 or 61, with isothianate 58 to synthesize N-hydroxythiourea compound 70 and with pentafluorophenylester 59 to synthesize compound 63, respectively.

Also, hydroxylamine compound 56 having 3-F group is condensed with isothiocyanate 26 to produce N-glemhydroxythiourea compound 64.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I) or (II) or a pharmaceutically acceptable salt thereof as an active ingredient for an antagonist of vanilloid receptor.

The compound of formula (I) or (II) according to the present invention has potent analgesic and anti-inflammatory activity, and the pharmaceutical composition of the present invention thus may be employed to alleviate or relieve acute, chronic or inflammatory pains or to suppress inflammation and to treat urgent urinary incontinence.

The present invention also provides a pharmaceutical composition comprising the compound selected from the group consisting of compounds of formula (I) or (II) or the pharmaceutical acceptable salts thereof for preventing and treating pain diseases or inflammatory diseases.

Pain diseases or inflammatory diseases comprise at least one selected from the group consisting of pain, acute pain, chronic pain, neuropathic pain, post-operative pain, migraine, arthralgia, neuropathies, nerve injury, diabetic neuropathy, neurodegeneration, neurotic skin disorder, stroke, urinary bladder hypersensitiveness, irritable bowel syndrome, a respiratory disorder such as asthma or chronic obstructive pulmonary disease, irritation of skin, eye or mucous membrane, fervescence, stomach-duodenal ulcer, inflammatory bowel disease and the like.

The present invention also provides a pharmaceutical composition comprising the compound selected from the group consisting of compounds of formula (I) or (II) or the pharmaceutical acceptable salts thereof for preventing and treating urgent urinary incontinence.
The pharmaceutical composition of the present invention comprises the inventive compounds between 0.0001 to 10% by weight, preferably 0.0001 to 1% by weight based on the total weight of the composition.

The present invention also provides an use of compound selected from the group consisting of compounds of formula (I) or (II) or the pharmaceutical acceptable salts thereof as antagonists of vanilloid receptors.

In accordance with another aspect of the present invention, there is also provided an use of the compound (I) or (II) for manufacture of medicines employed for alleviating or treating pain, acute pain, chronic pain, neuropathic pain, post-operative pain, migraine, arthralgia, neuropathies, nerve injury, diabetic neuropathy, neurodegeneration, neurotic skin disorder, stroke, urinary bladder hypersensitiveness, irritable bowel syndrome, a respiratory disorder such as asthma or chronic obstructive pulmonary disease, irritation of skin, eye or mucous membrane, fervescence, stomach-duodenal ulcer, inflammatory bowel disease, inflammatory disease or urgent urinary incontinence.

The compound of formula (I) or (II) according to the present invention can be provided as a pharmaceutical composition comprising pharmaceutically acceptable carriers, adjuvants or diluents. For example, the compounds of the present invention can be dissolved in oils, propylene glycol or other solvents, which are commonly used to produce an injection. Suitable examples of the carriers include physiological saline, polyethylene glycol, ethanol, vegetable oils, isopropyl myristate, etc., but are not limited to them. For topical administration, the compounds of the present invention can be formulated in the form of ointments and creams.

In accordance with another aspect of the present invention, there is also provided an method of alleviating or treating pain, acute pain, chronic pain, neuropathic pain, post-operative pain, migraine, arthralgia, neuropathies, nerve injury, diabetic neuropathy, neurodegeneration, neurotic skin disorder, stroke, urinary bladder hypersensitiveness, irritable bowel syndrome, a respiratory disorder such as asthma or chronic obstructive pulmonary disease, irritation of skin, eye or mucous membrane, fervescence, stomach-duodenal ulcer, inflammatory bowel disease, inflammatory disease or urgent urinary incontinence, wherein the method comprises administering a therapeutically effective amount of the compound of formula of (I) or (II) or the pharmaceutically acceptable salt thereof.

Hereinafter, the following formulation methods and excipients are merely exemplary and in no way limit the invention.

The compounds of the present invention in pharmaceutical dosage forms may be used in the form of their pharmaceutically acceptable salts, and also may be used alone or in appropriate association, as well as in combination with other pharmaceutically active compounds.

The compounds of the present invention may be formulated into preparations for injections by dissolving, suspending, or emulsifying them in aqueous solvents such as normal saline, 5% Dextrose, or non-aqueous solvent such as vegetable oil, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol. The formulation may include conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives.

The desirable dose of the inventive compounds varies depending on the condition and the weight of the subject, severity, drug form, route and period of administration, and may be chosen by those skilled in the art. However, in order to obtain desirable effects, it is generally recommended to administer at the amount ranging 0.0001 - 100 mg/kg, preferably 0.001 – 100 mg/kg by weight/day of the inventive compounds of the present invention. The dose may be administered in single or divided into several times per day. In terms of composition, the compounds should be present between 0.0001 to 10% by weight, preferably 0.0001 to 1% by weight based on the total weight of the composition.

The pharmaceutical composition of present invention can be administered to a subject animal such as mammals (rat, mouse, domestic animals or human) via various routes. All modes of administration are contemplated, for example, administration can be made orally, rectally or by intravenous, intramuscular, subcutaneous, intrathecal, epidural or intracerebroventricular injection.

It is another object of the present invention to provide a use of the above-mentioned compound of the present invention for the preparation of therapeutic agent for the preventing and treating pain disease or inflammatory disease by showing vanilloid receptor-antagonistic activity in human or mammal.

Additionally, it is an object of the present invention to provide a method of treating or preventing pain disease and inflammatory disease by showing vanilloid receptor-antagonistic activity in a mammal comprising administering to said mammal an effective amount of the above-mentioned compound of the present invention together with a pharmaceutically acceptable carrier thereof.

It will be apparent to those skilled in the art that various modifications and variations can be made in the compositions, use and preparations of the present invention without departing from the spirit or scope of the invention.

Brief Description of the Drawings

The above and other objects, features and other advantages of the present invention will more clearly understood from the following detailed description taken in conjunction with the accompanying drawings, in which;

Fig. 1 shows the analgesic effect of thiourea compounds in prior art (JYL-827, JYL-1433) and N-hydroxy thiourea compound 35 (SU-66) and 37 (SU-154) in acetic acid-induced writhing test.

Examples

The present invention is more specifically explained by the following examples. However, it should be understood that the present invention is not limited to these examples in any manner.

Example 1 : Preparation of *tert*-butyl-N-[(*tert*-butoxycarbonyl)oxy]-N-(4-*tert*-butylbenzyl)carbamate compound (2)

A cooled solution of *tert*-butyl-N-(*tert*-butoxycarbonyloxy)carbamate (5 g, 21.4 mmol) in DMF (20 ㎖) at 0 °C was treated with sodium hydride (60%, 12.8 g, 21.4 mmol) portionwisely and stirred for 30 min at room temperature. The reaction mixture was added to 4-*tert*-butylbenzyl bromide (7.3g, 32.1 mmol) and stirred for 18 hrs at room temperature. The mixture was diluted with H_2O and extracted with EtOAc several times. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on Silica gel with EtOAc/hexanes (10:1) solvent mixture as an eluant to give 7.72 g of colorless *tert*-butyl-N-[(*tert*-butoxycarbonyl)oxy]-N-(4-*tert*-butylbenzyl) carbamate 2 (yield : 95%).

^{1}H-NMR ($CDCl_3$) δ: 7.35 (dt, 2 H, J = 2.2, 8.5 Hz, Ar), 7.26 (d, 2 H, J = 8.5 Hz, Ar), 4.72 (s, 2 H, CH_2), 1.49 (s, 9 H, $C(CH_3)_3$), 1.44 (s, 9 H, $C(CH_3)_3$), 1.30 (s, 9 H, $C(CH_3)_3$).

Example 2 : Preparation of N-[4-*tert*-butylbenzyl]hydroxylamine compound (3)

A cooled solution of *tert*-butyl-N-[(*tert*-butoxycarbonyl)oxy]-N-(4-*tert*-butylbenzyl)carbamate of Example 1 (7.6g, 20 mmol) in CH_2Cl_2 (100 ㎖) at 0 °C was treated with trifluoroacetic acid (20 ㎖) and stirred for 50 mins at room temperature. The mixture was

concentrated *in vacuo* below 20 °C to remove the solvent. The residue was fractionated with saturated sodium bicarbonate and diethyl ester solution and the water soluble layer thereof was extracted with diethyl ester solution. The organic layers were washed with water and saline, dried over $MgSO_4$ and concentrated *in vacuo* to give 3.58 g of yellow oil of N-[4-*tert*-butylbenzyl]hydroxylamine 3 (yield : 100%).

^{1}H-NMR ($CDCl_3$) δ: 7.39 (d, 2 H, J = 8.0 Hz, Ar), 7.27 (d, 2 H, J = 8.0 Hz, Ar), 4.22 (s, 2 H, CH_2), 1.27 (s, 9 H, $C(CH_3)_3$).

Example 3 : Preparation of *tert*-butyl-N-[(*tert*-butoxycarbonyl)oxy]-N-[2-(3,4-dimethylbenzyl)-3-pivaloyloxy-propyl] carbamate compound (6)

A solution of *tert*-butyl N-(*tert*-butoxycarbonyloxy)carbamate (0.92 g, 3.95 mmol) in THF (30 ㎖) was mixed with diethyl azodicarboxylate (0.85 ㎖, 5.39 mmol) slowly and stirred for 5 mins at room temperature. The mixture was reacted by the dropwise addition of triphenylphospine (1.41 g, 5.39 mmol) and above-mentioned compound 4 (1 g, 3.59 mmol) and stirred for 30 mins at room temperature. The reaction was stopped by adding 5㎖ of methanol and the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on Silica gel with EtOAc/hexanes (1:10) solvent mixture as an eluant to give 1.6g of colorless oil of *tert*-butyl N-[(*tert*-butoxylcarbonyl)oxy]-N-[2-(3,4-dimethylbenzyl)-3-pivaloyloxy-propyl]carbamate compound 6 (yield : 90%).

^{1}H-NMR ($CDCl_3$) δ: 6.85-7.05 (m, 3 H, Ar), 3.9-4.1 (m, 2 H, CH_2OCO), 3.67 (bs, 2 H, CH_2N), 2.5-2.9 (m, 2 H, CH_2Ar), 2.18-2.28 (m, 7 H, 2 x CH_3 & CH), 1.53 (s, 9 H, $C(CH_3)_3$), 1.47 (s, 9 H, $C(CH_3)_3$), 1.22 (s, 9 H, $C(CH_3)_3$)

Example 4 : Preparation of *tert*-butyl-N-[(*tert*-butoxycarbonyl)oxy]-N-[2-(4-*tert*-butylbenzyl)-3-pivaloyloxy-propyl] carbamate compound (7)

The compound 7 was prepared by the same procedure described in above Example 3 excepting using compound 5 to give 1.45 g of *tert*-butyl-N-[(*tert*-butoxycarbonyl)oxy]-N-[2-(4-*tert*-butylbenzyl)-3-pivaloyloxy-propyl] carbamate 7 (yield : 90%).

^{1}H-NMR ($CDCl_3$) δ: 7.29 (d, 2 H, J = 8.3 Hz, Ar), 7.09 (d, 2 H, J = 8.3 Hz, Ar), 4.00 (ddd of AB, 2 H, CH_2OCO), 3.66 (bs, 2 H, CH_2N), 2.79 (dd, 1 H, CH_2Ar), 2.60 (dd, 1 H, CH_2Ar), 2.30 (m, 1 H, CH), 1.52 (s, 9 H, $C(CH_3)_3$), 1.47 (s, 9 H, $C(CH_3)_3$), 1.30 (s, 9 H, $C(CH_3)_3$), 1.22 (s, 9 H, $C(CH_3)_3$)

Example 5 : Preparation of N-[2-(3,4-dimethylbenzyl)-3-pivaloyloxy-propyl] hydroxylamine compound (8)

The compound 8 was prepared by the same procedure described in above Example 2 excepting using compound *tert*-butyl-N-[(*tert*-butoxycarbonyl)oxy]-N-[2-(3,4-dimethylbenzyl)-3-pivaloyloxy-propyl]carbamate compound 6 to give 1.6 g of N-[2-(3,4-dimethylbenzyl)-3-pivaloyloxy-propyl] hydroxylamine 8 (yield : 90%).

^{1}H-NMR($CDCl_3$) δ: 6.86-7.06 (m, 3 H, Ar), 5.45 (bs, 1 H), 3.95-4.15 (m, 2 H, CH_2OCO), 2.85-3.02 (m, 2 H, CH_2N), 2.72 (d, 1 H, CH_2Ar), 2.62 (m, 1 H, CH_2Ar), 2.2-2.4 (m, 7 H, 2 x CH_3 & CH)

Example 6 : Preparation of N-[2-(4-*tert*-butylbenzyl)-3-pivaloyloxy-propyl] hydroxylamine compound (9)

The compound 9 was prepared by the same procedure described in above Example 2 excepting using compound *tert*-butyl-N-[(*tert*-butoxycarbonyl)oxy]-N-[2-(4-*tert*-butylbenzyl)-3-pivaloyloxy-propyl]carbamate compound 7 to give 1.45 g of N-[2-(4-butylbenzyl)-3-pivaloyloxy-propyl] hydroxylamine 9 (yield : 88%).

^{1}H-NMR ($CDCl_3$) δ: 7.30 (d, 2 H, J = 8.2 Hz), 7.10 (d, 2 H, J = 8.2 Hz), 5.16 (bs, 1 H), 4.06 (ddd of AB, 2 H, J = 5, 11.2 Hz, CH_2OCO), 2.95 (ddd of AB, 2 H, J = 6, 13 Hz, CH_2N), 2.67 (ddd of AB, 2 H, J = 7, 13.5 Hz, CH_2Ar), 2.33 (m, 1 H, CH), 2.2-2.4 (m, 7 H, 2 x CH_3), 1.30 (s, 9 H, $C(CH_3)_3$), 1.22 (s, 9 H, $C(CH_3)_3$)

Example 7 : General Method of isothiocyanate synthesis

A mixture of azide (1.0 mmol), triphenylphosphine (290 mg, 1.1 mmol) in THF (10 mℓ) was treated with sodium hydride (NaH) (0.6 mℓ, 10 mmol), refluxed for 1 to 3 hours and concentrated *in vacuo*. The residue was purified by column chromatography with EtOAc/hexanes (1:2) solvent mixture as an eluant to give isothiocyanate compound.

Example 8 : Preparation of 4-(methylsulfonylamino)benzyl isothiocyanate compound (17)

The white solid 4-(methylsulfonylamino)benzyl isothiocyanate compound 17 (yield : 63%) was prepared by the same procedure described in above Example 7.

melting point : 122-124 °C

^{1}H-NMR($CDCl_3$) δ: 7.32 (d, 2 H, J = 8.4 Hz) 7.24 (d, 2 H, J = 8.4 Hz), 6.62 (s, 1 H, $NHSO_2$), 4.70 (s, 2 H, CH_2) 3.04 (s, 3 H, SO_2CH_3)

Example 9 : Preparation of 3-methoxy-4-(methylsulfonylamino)benzyl isothiocyanate compound (18)

The 3-methoxy-4-(methylsulfonylamino)benzyl isothiocyanate compound 18 (yield : 59%) was prepared by the same procedure described in above Example 7.

melting point : 100-103 °C

^{1}H-NMR($CDCl_3$) δ: 7.53 (d, 1 H, J = 8.2 Hz), 6.88-6.92 (m, 2 H), 6.80 (bs, 1 H, $NHSO_2$), 4.68 (s, 2 H, CH_2), 3.92 (s, 3 H, OCH_3), 2.97 (s, 3 H, SO_2CH_3)

Example 10 : Preparation of 3-fluoro-4-(methylsulfonylamino)benzyl isothiocyanate compound (19)

The 3-fluoro-4-(methylsulfonylamino)benzyl isothiocyanate compound 19 (yield : 54%) was prepared by the same procedure described in above Example 7.

melting point : 95 - 97°C

^{1}H-NMR($CDCl_3$) δ: 7.61 (t, 1 H, J = 8.0 Hz), 7.14 (m, 2 H), 6.53 (bs, 1 H, $NHSO_2$), 4.70 (s, 2 H, CH_2), 3.01 (s, 3 H, SO_2CH_3)

Example 11 : Preparation of 3-chloro-4-(methylsulfonylamino)benzyl isothiocyanate compound (20)

The 3-chloro-4-(methylsulfonylamino)benzyl isothiocyanate compound 20 (yield : 48%) was prepared by the same procedure described in above Example 7.

melting point : 112 - 113°C

^{1}H-NMR($CDCl_3$) δ: 7.68 (d, 1 H, J = 8.3 Hz), 7.42 (d, 1 H, J = 2.4 Hz), 7.26 (dd, 1 H, J = 8.3, 2.4 Hz), 6.80 (bs, 1 H, $NHSO_2$), 4.70 (s, 2 H, CH_2), 3.04 (s, 3 H, SO_2CH_3)

Example 12 : Preparation of 4-(methylsulfonylamino)-3-nitrobenzyl isothiocyanate compound (21)

The 4-(methylsulfonylamino)-3-nitrobenzyl isothiocyanate compound 21 (yield : 42%) was prepared by the same procedure described in above Example 7.

melting point : 128 - 130°C

^{1}H-NMR($CDCl_3$) δ: 8.24 (d, 1 H, J = 2.4 Hz), 7.95 (d, 1 H, J = 8.3 Hz), 7.66 (dd, 1 H, J = 8.3, 2.4 Hz), 4.78 (s, 2 H, CH_2), 3.18 (s, 3 H, SO_2CH_3)

Example 13 : Preparation of 2-fluoro-4-(methylsulfonylamino)benzyl isothiocyanate compound (22)

The 2-fluoro-4-(methylsulfonylamino)benzyl isothiocyanate compound 22 (yield : 56%) was prepared by the same procedure described in above Example 7.

^{1}H-NMR($CDCl_3$) δ: 7.38 (t, 1 H, J = 8.0 Hz), 7.09 (dd, 1 H, J = 10.9, 2.2 Hz), 6.99 (dd, 1 H, J = 8.3, 2.2 Hz), 4.73 (s, 2 H, CH_2), 3.08 (s, 3 H, SO_2CH_3)

Example 14 : Preparation of 2-chloro-4-(methylsulfonylamino)benzyl isothiocyanate compound (23)

The 2-fluoro-4-(methylsulfonylamino)benzyl isothiocyanate compound 23 (yield : 54%) was prepared by the same procedure described in above Example 7.

melting point : 110 - 112°C

^{1}H-NMR ($CDCl_3$) δ: 7.43 (d, 1 H, J = 8.3 Hz), 7.33 (d, 1 H, J = 2.2 Hz), 7.16 (dd, 1 H, , J = 8.3 and 2.2 Hz), 6.79 (bs, 1 H, $NHSO_2$), 4.79 (s, 2 H, CH_2), 3.08 (s, 3 H, SO_2CH_3)

Example 15 : Preparation of 2-(3,4-dimethylbenzyl)-3-pivaloyloxy-propyl isothiocyanate compound (26)

The colorless oil of 2-(3,4-dimethylbenzyl)-3-pivaloyloxy propyl isothiocyanate compound 26 (yield : 92%) was prepared by the same procedure described in above Example 7.

^{1}H-NMR($CDCl_3$) δ: 6.85-7.1 (m, 3 H, Ar), 3.95-4.2 (m, 2 H, CH_2OCO), 3.53 (m, 2 H, CH_2NCS), 2.55-2.85 (m, 2 H, CH_2Ar), 2.2-2.3 (m, 7 H, 2 x CH_3 and CH), 1.23 (s, 9 H, $C(CH_3)_3$)

Example 16 : Preparation of 2-(4-*tert*-butylbenzyl)-3-pivaloyloxy-propyl isothiocyanate compound (27)

The colorless oil of 2-(4-*tert*-butylbenzyl)-3-pivaloyloxy-propyl isothiocyanate compound 27 (yield : 90%) was prepared by the same procedure described in above Example 7.

^{1}H-NMR($CDCl_3$) δ: 7.33 (d, 2 H, J = 8.3 Hz), 7.10 (d, 2 H, J = 8.3 Hz), 4.15 (dd, 1 H, J = 4.9 , 11.4 Hz, CH_2OCO), 4.01 (dd, 1 H, J = 7 , 11.4 Hz, CH_2OCO), 3.53 (sevenlet, 2 H, CH_2NCS), 2.70 (ddd of AB, 2 H, CH_2Ar), 2.31 (bs, 1 H, CH), 1.31 (s, 9 H, $C(CH_3)_3$), 1.23 (s, 9 H, $C(CH_3)_3$).

Example 17 : General Method of N-hydroxythiourea compound synthesis

A mixture of hydroxylamine (1.0 mmol), isothiocyanate (1.0 mmol) in CH_2Cl_2 (10 mℓ) was stirred for 1 to 4 hours at room temperature and concentrated *in vacuo*. The residue was purified by column chromatography with EtOAc/hexanes (1:2) solvent mixture as an eluant to give N-hydroxythiourea compound.

Example 18 : Preparation of N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[4-(methylsulfonylamino)benzyl]thiourea compound (28)

The mixture of compound 17 and 3 was treated according to the same procedure described in above Example 17 to give white solid of N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[4-(methylsulfonylamino)benzyl]thiourea compound 28 (yield : 94%).

melting point : 137°C

^{1}H-NMR($CDCl_3$) δ: 7.38 (s, 4 H), 7.32 (d, 2 H, J = 8.3 Hz), 7.15 (d, 2 H, J = 8.3 Hz), 6.46 (s, 1 H, $NHSO_2$), 5.97 (bs, 1 H, NHCS), 5.34 (s, 2 H, CH_2NOH), 4.82 (d, 2 H, J = 5.6 Hz, $NHCH_2$), 2.97 (s, 3 H, SO_2CH_3), 1.31 (s, 9 H, $C(CH_3)_3$)

IR (KBr): 3350, 2962, 1512, 1336, 1123 cm^{-1}

MS *m/z* : 422 (MH^+)

Example 19 : Preparation of N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[3-methoxy-4-(methylsulfonylamino)benzyl]thiourea compound (29)

The mixture of compound 18 and 3 was treated according to the same procedure described in above Example 17 to give white solid of N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[3-methoxy-4-(methylsulfonylamino)benzyl]thiourea compound 29 (yield : 92%) (*See* Table 1).

melting point : 112.5-115°C

^{1}H-NMR ($CDCl_3$) δ: 7.39 (m, 4 H), 6.99 (m, 1 H), 6.91 (m, 1 H), 6.74 (m, 1 H), 5.52 (bs, 1 H, NH), 5.36 (s, 2 H, CH_2NHOH), 4.83 (d, 2 H, J = 5.6 Hz, CH_2NH), 3.88 (s, 3 H, OCH_3), 2.94 (s, 3 H, SO_2CH_3), 1.32 (s, 9 H, $C(CH_3)_3$)

IR (KBr) 3352, 2962, 1513, 1336, 1123 cm^{-1}

MS *m/z*: 452 (MH^+)

Example 20 : Preparation of N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[3-fluoro-4-(methylsulfonylamino)benzyl]thiourea compound (30)

The mixture of compound 19 and 3 was treated according to the same procedure described in above Example 17 to give N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[3-fluoro-4-(methylsulfonylamino)benzyl]thiourea compound 30 (yield : 93%) (*See* Table 1).

melting point : 124-126°C

^{1}H-NMR($CDCl_3$) δ: 7.50 (t, 1 H, J = 8.0 Hz), 7.38 (AB q, 4 H, J = 8.8 Hz), 7.1-7.2 (m, 2 H), 5.34 (s, 2 H, CH_2NOH), 4.85 (d, 2 H, J = 5.6 Hz, CH_2NH), 3.00 (s, 3 H, SO_2CH_3), 1.32 (s, 9 H, $C(CH_3)_3$)

IR (KBr): 3260, 2963, 1513, 1326, 1153, 1107 cm^{-1}

MS *m/z* : 440 (MH^+)

Example 21 : Preparation of N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[3-chloro-4-(methylsulfonylamino)benzyl]thiourea compound (31)

The mixture of compound 20 and 3 was treated according to the same procedure described in above Example 17 to give N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[3-chloro-4-(methylsulfonylamino)benzyl]thiourea compound 31 (yield : 91%) (*See* Table 1).

melting point : 119.5-122.5°C

^{1}H-NMR($CDCl_3$) δ: 7.62 (d, 1 H, J = 8.5 Hz), 7.44 (d, 1 H, J = 2.0 Hz), 7.36-7.42 (m, 3 H), 7.26 (m, 2 H), 5.36 (s, 2 H, $HONCH_2$), 4.86 (d, 2 H, J = 5.8 Hz, $NHCH_2$), 3.01 (s, 3 H, SO_2CH_3), 1.32 (s, 9 H, $C(CH_3)_3$).

IR (KBr): 3400, 2919, 1737, 1383, 1216, 1107 cm^{-1}

MS *m/z* 456 (MH^+)

Example 22 : Preparation of N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[4-(methylsulfonylamino)-3-nitrobenzyl]thiourea compound (32)

The mixture of compound 21 and 3 was treated according to the same procedure described in above Example 17 to give N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[4-(methylsulfonylamino)-3-nitrobenzyl]thiourea compound 32 (yield : 90%)(*See* Table 1).

melting point : 102-105°C

^{1}H-NMR ($CDCl_3$) δ: 8.22 (d, 1 H, J = 2.0 Hz, ArH-2), 7.86 (d, 1 H, J = 8.3 Hz, ArH-5), 7.70 (dd, 1 H, J = 2.0, 8.3 Hz, ArH-6), 7.40 (dd, 4 H, Ar), 5.36 (s, 2 H, $HONCH_2$), 4.92 (d, 2 H, J = 5.6 Hz, $NHCH_2$), 3.14 (s, 3 H, SO_2CH_3), 1.32 (s, 9 H, $C(CH_3)_3$)

IR (KBr) 3360, 2919, 1538, 1337, 1143 cm^{-1}

MS *m/z*: 467 (MH^+)

Example 23 : Preparation of N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[2-fluoro-4-(methylsulfonylamino)benzyl]thiourea compound (33)

The mixture of compound 22 and 3 was treated according to the same procedure described in above Example 17 to give N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[2-fluoro-4-(methylsulfonylamino)benzyl]thiourea compound 33 (yield : 96%) (*See* Table 1).

melting point : 136-137°C

^{1}H-NMR($CDCl_3$) δ: 7.44 (t, 1 H, J = 8.3 Hz), 7.38 (AB q, 4 H), 7.01 (dd, 1 H, J = 11.2, 2.2 Hz), 6.86 (dd, 1 H, J = 8.3, 2.2 Hz), 6.52 (s, 1 H, $NHSO_2$), 5.75 (s, 1 H, NH), 5.32 (s, 2 H, CH_2NOH), 4.87 (d, 2 H, J = 5.8 Hz, CH_2NH), 3.00 (s, 3 H, SO_2CH_3), 1.31 (s, 9 H, $C(CH_3)_3$).

IR (KBr): 3266, 2962, 1532, 1325, 1148, 1109 cm^{-1}

MS *m/z*: 440 (MH^+)

Example 24 : Preparation of N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[2-chloro-4-(methylsulfonylamino)benzyl]thiourea compound (34)

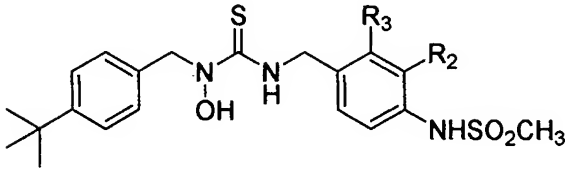
The mixture of compound 23 and 3 was treated according to the same procedure described in above Example 17 to give N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[2-chloro-4-(methylsulfonylamino)benzyl]thiourea compound 34 (yield : 95%) (*See* Table 1).

melting point : 150-152°C

^{1}H-NMR($CDCl_3$) δ: 7.50 (d, 1 H, J = 8.5 Hz), 7.35 (dd, 4 H, J = 3.4, 12.2 Hz), 7.29 (d, 1 H, J = 2.2 Hz), 7.04 (dd, 1 H, , J = 8.3 and 2.2 Hz), 5.32 (s, 2 H, $HONCH_2$), 4.92 (d, 2 H, J = 6.1 Hz, $NHCH_2$), 3.02 (s, 3 H, SO_2CH_3), 1.31 (s, 9 H, $C(CH_3)_3$)

IR (KBr): 3400, 2919, 1737, 1383, 1216, 1107 cm^{-1}

MS *m/z*: 456 (MH^+)



(VII)

Table 1

Group	Compound	R_2	R_3	Yield (%)	Spectrum data
III	28	H	H	94	^{1}H-NMR($CDCl_3$) δ: 7.38 (s, 4 H), 7.32 (d, 2 H, J = 8.3 Hz), 7.15 (d, 2 H, J = 8.3 Hz), 6.46 (s, 1 H, $NHSO_2$), 5.97 (bs, 1 H, NHCS), 5.34 (s, 2 H, CH_2NOH), 4.82 (d, 2 H, J = 5.6 Hz, $NHCH_2$), 2.97 (s, 3 H, SO_2CH_3), 1.31 (s, 9 H, $C(CH_3)_3$)
	29	OCH_3	H	92	^{1}H-NMR ($CDCl_3$) δ: 7.39 (m, 4 H), 6.99 (m, 1 H), 6.91 (m, 1 H), 6.74 (m, 1 H), 5.52 (bs, 1 H, NH), 5.36 (s, 2 H, CH_2NHOH), 4.83 (d, 2 H, J = 5.6 Hz, CH_2NH), 3.88 (s, 3 H, OCH_3), 2.94 (s, 3 H, SO_2CH_3), 1.32 (s, 9 H, $C(CH_3)_3$)
	30	F	H	93	^{1}H-NMR($CDCl_3$) δ: 7.50 (t, 1 H, J = 8.0 Hz), 7.38 (AB q, 4 H, J = 8.8 Hz), 7.1-7.2 (m, 2 H), 5.34 (s, 2 H, CH_2NOH), 4.85 (d, 2 H, J = 5.6 Hz, CH_2NH), 3.00 (s, 3 H, SO_2CH_3), 1.32 (s, 9 H, $C(CH_3)_3$)

	31	Cl	H	91	^{1}H-NMR($CDCl_3$) δ: 7.62 (d, 1 H, J = 8.5 Hz), 7.44 (d, 1 H, J = 2.0 Hz), 7.36-7.42 (m, 3 H), 7.26 (m, 2 H), 5.36 (s, 2 H, $HONCH_2$), 4.86 (d, 2 H, J = 5.8 Hz, $NHCH_2$), 3.01 (s, 3 H, SO_2CH_3), 1.32 (s, 9 H, $C(CH_3)_3$)
	32	NO_2	H	90	^{1}H-NMR ($CDCl_3$) δ: 8.22 (d, 1 H, J = 2.0 Hz, ArH-2), 7.86 (d, 1 H, J = 8.3 Hz, ArH-5), 7.70 (dd, 1 H, J = 2.0, 8.3 Hz, ArH-6), 7.40 (dd, 4 H, Ar), 5.36 (s, 2 H, $HONCH_2$), 4.92 (d, 2 H, J = 5.6 Hz, $NHCH_2$), 3.14 (s, 3 H, SO_2CH_3), 1.32 (s, 9 H, $C(CH_3)_3$)
	33	H	F	96	^{1}H-NMR($CDCl_3$) δ: 7.44 (t, 1 H, J = 8.3 Hz), 7.38 (AB q, 4 H), 7.01 (dd, 1 H, J = 11.2, 2.2 Hz), 6.86 (dd, 1 H, J = 8.3, 2.2 Hz), 6.52 (s, 1 H, $NHSO_2$), 5.75 (s, 1 H, NH), 5.32 (s, 2 H, CH_2NOH), 4.87 (d, 2 H, J = 5.8 Hz, CH_2NH), 3.00 (s, 3 H, SO_2CH_3), 1.31 (s, 9 H, $C(CH_3)_3$)

	34	H	Cl	95	^{1}H-NMR($CDCl_3$) δ: 7.50 (d, 1 H, J = 8.5 Hz), 7.35 (dd, 4 H, J = 3.4, 12.2 Hz), 7.29 (d, 1 H, J = 2.2 Hz), 7.04 (dd, 1 H, , J = 8.3 and 2.2 Hz), 5.32 (s, 2 H, $HONCH_2$), 4.92 (d, 2 H, J = 6.1 Hz, $NHCH_2$), 3.02 (s, 3 H, SO_2CH_3), 1.31 (s, 9 H, $C(CH_3)_3$)

Example 25. Preparation of N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[4-(methylsulfonylamino)benzyl]thiourea compound(35)

The mixture of compound 17 and 8 was treated according to the same procedure described in above Example 17 to give white solid of N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy) propyl]-N-hydroxy-N-[4-(methylsulfonylamino)benzyl]thiourea compound 35 (yield : 94%) (*See* Table 2).

melting point : 120-123°C

^{1}H-NMR($CDCl_3$) δ: 7.63 (bs, 1 H, NH), 7.28 (d, 2 H, J = 8.3 Hz), 7.15 (d, 2 H, J = 8.3 Hz), 6.8-7.1 (m, 4 H, Ph and NH), 4.74 (d, 2 H, J = 5.6 Hz, $NHCH_2Ar$), 3.95-4.25 (m, 4 H, CH_2OCO, CH_2NOH), 2.96 (s, 3 H, SO_2CH_3), 2.5-2.75 (m, 3 H, $CHCH_2Ar$), 2.24 (d, 6 H, 2 x CH_3), 1.20 (s, 9 H, $C(CH_3)_3$)

IR (KBr): 3266, 1698, 1539, 1337, 1154 cm^{-1}

Mass *m/z*: 536 (MH^+)

Example 26. Preparation of N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[3-methoxy-4-(methylsulfonylamino)benzyl]thiourea compound(36)

The mixture of compound 18 and 8 was treated according to the same procedure described in above Example 17 to give N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[3-methoxy-4-(methylsulfonylamino)benzyl] thiourea compound 36 (yield : 90%) (*See* Table 2).

^{1}H-NMR($CDCl_3$) δ: 7.47 (d, 1 H, J = 8.0 Hz), 6.88-7.06 (m, 5 H), 6.74 (s, 1 H, $NHSO_2$), 4.77 (d, 2 H, CH_2NOH), 4.1-4.25 (m, 3 H, CH_2NH and CH_2OCO), 4.00 (AB q, 1 H, J = 5.4 Hz, CH_2OCO), 3.87 (s, 3 H, OCH3), 2.94 (s, 3 H, SO_2CH_3), 2.5-2.7 (m, 3 H, CH_2Ar and CH), 2.2-2.3 (m, 6 H, 2 x CH_3), 1.18 (s, 9 H, $C(CH_3)_3$)

IR (KBr): 3334, 2921, 1716 cm^{-1}

MS *m/z*: 566 (MH^+)

Example 27. Preparation of N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[3-fluoro-4-(methylsulfonylamino)benzyl]thiourea compound(37)

The mixture of compound 19 and 8 was treated according to the same procedure described in above Example 17 to give N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[3-fluoro-4-(methylsulfonylamino)benzyl]thiourea compound 37 (yield : 93%) (*See* Table 2).

melting point : 52-55 °C

^{1}H-NMR($CDCl_3$) δ: 7.74 (bs, 1 H), 7.64 (bs, 1 H), 7.52 (t, 1 H, J = 8.3 Hz), 6.9-7.25 (m, 5 H), 6.45 (bs, 1 H, $NHSO_2$), 4.81 (d, 2 H, J = 3.7 Hz, $NHCH_2Ar$), 4.18 (m, 3 H, CH_2NOH and CH_2OCO), 4.00 (dd, 1 H, CH_2OCO), 3.01 (s, 3 H, SO_2CH_3), 2.5-2.8 (m, 3 H, $CHCH_2Ph$), 2.2-2.3 (m, 6 H, 2 x CH_3), 1.19 (s, 9 H, $C(CH_3)_3$)

IR (KBr): 3362, 2971, 1715, 1508, 1337, 1158 cm^{-1}

MS *m/z*: 554 (MH^+)

Example 28. Preparation of N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[2-fluoro-4-(methylsulfonylamino)benzyl]thiourea compound(38)

The mixture of compound 22 and 8 was treated according to the same procedure described in above Example 17 to give N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[2-fluoro-4-(methylsulfonylamino)benzyl]thiourea compound 38 (yield : 91%) (*See* Table 2).

melting point : 55-57 °C

^{1}H-NMR($CDCl_3$) δ: 7.39 (t, 1 H, J = 8.0 Hz), 7.85-7.05 (m, 5 H), 6.9-7.25 (m, 5 H), 4.81 (d, 2 H, J = 5.6 Hz, $NHCH_2Ar$), 3.95-4.25 (m, 4 H, CH_2NOH and CH_2OCO), 3.00 (s, 3 H, SO_2CH_3), 2.5-2.8 (m, 3 H, $CHCH_2Ph$), 2.2-2.3 (m, 6 H, 2 x CH_3), 1.19 (s, 9 H, $C(CH_3)_3$)

IR (KBr): 3254, 2971, 1701, 1626, 1530, 1331, 1149 cm^{-1}

MS *m/z* : 554 (MH^+)

Example 29. Preparation of N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[2-chloro-4-(methylsulfonylamino)benzyl]thiourea compound(39)

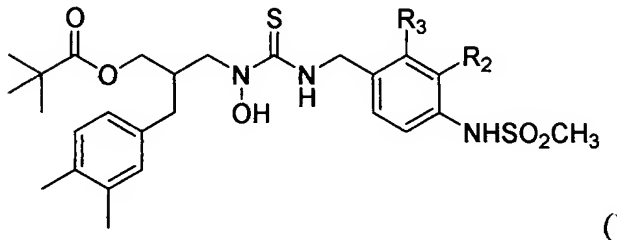
The mixture of compound 23 and 8 was treated according to the same procedure described in above Example 17 to give N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[2-chloro-4-(methylsulfonylamino)benzyl]thiourea compound 39 (yield : 94%) (*See* Table 2).

melting point : 56-58 °C

^{1}H-NMR($CDCl_3$) δ: 7.35-7.45 (m, 2 H), 6.9-7.05 (m, 4 H), 4.85 (d, 2 H, J = 6.1 Hz, $NHCH_2Ar$), 3.95-4.25 (m, 4 H, CH_2NOH and CH_2OCO), 2.99 (s, 3 H, SO_2CH_3), 2.5-2.8 (m, 3 H, $CHCH_2Ph$), 2.2-2.3 (m, 6 H, 2 x CH_3), 1.20 (s, 9 H, $C(CH_3)_3$)

IR (KBr): 3262, 2972, 1698, 1608, 1531, 1325, 1156 cm^{-1}

MS *m/z* : 570(MH^+)



(VIII)

Table 2

Group	Compound	R_2	R_3	Yield (%)	Spectrum data
III	35	H	H	94	^{1}H-NMR($CDCl_3$) δ: 7.63 (bs, 1 H, NH), 7.28 (d, 2 H, J = 8.3 Hz), 7.15 (d, 2 H, J = 8.3 Hz), 6.8-7.1 (m, 4 H, Ph and NH), 4.74 (d, 2 H, J = 5.6 Hz, $NHCH_2Ar$), 3.95-4.25 (m, 4 H, CH_2OCO, CH_2NOH), 2.96 (s, 3 H, SO_2CH_3), 2.5-2.75 (m, 3 H, $CHCH_2Ar$), 2.24 (d, 6 H, 2 x CH_3), 1.20 (s, 9 H, $C(CH_3)_3$)
	36	OCH_3	H	90	^{1}H-NMR($CDCl_3$) δ: 7.47 (d, 1 H, J = 8.0 Hz), 6.88-7.06 (m, 5 H), 6.74 (s, 1 H, $NHSO_2$), 4.77 (d, 2 H, CH_2NOH), 4.1-4.25 (m, 3 H, CH_2NH and CH_2OCO), 4.00 (AB q, 1 H, J = 5.4 Hz, CH_2OCO), 3.87 (s, 3 H, OCH3), 2.94 (s, 3 H, SO_2CH_3), 2.5-2.7 (m, 3 H, CH_2Ar and CH), 2.2-2.3 (m, 6 H, 2 x CH_3), 1.18 (s, 9 H, $C(CH_3)_3$)

	37	F	H	93	^{1}H-NMR($CDCl_3$) δ: 7.74 (bs, 1 H), 7.64 (bs, 1 H), 7.52 (t, 1 H, J = 8.3 Hz), 6.9-7.25 (m, 5 H), 6.45 (bs, 1 H, $NHSO_2$), 4.81 (d, 2 H, J = 3.7 Hz, $NHCH_2Ar$), 4.18 (m, 3 H, CH_2NOH and CH_2OCO), 4.00 (dd, 1 H, CH_2OCO), 3.01 (s, 3 H, SO_2CH_3), 2.5-2.8 (m, 3 H, $CHCH_2Ph$), 2.2-2.3 (m, 6 H, 2 x CH_3), 1.19 (s, 9 H, $C(CH_3)_3$)
	38	H	F	91	^{1}H-NMR($CDCl_3$) δ: 7.39 (t, 1 H, J = 8.0 Hz), 7.85-7.05 (m, 5 H), 6.9-7.25 (m, 5 H), 4.81 (d, 2 H, J = 5.6 Hz, $NHCH_2Ar$), 3.95-4.25 (m, 4 H, CH_2NOH and CH_2OCO), 3.00 (s, 3 H, SO_2CH_3), 2.5-2.8 (m, 3 H, $CHCH_2Ph$), 2.2-2.3 (m, 6 H, 2 x CH_3), 1.19 (s, 9 H, $C(CH_3)_3$)
	39	H	Cl	94	^{1}H-NMR($CDCl_3$) δ: 7.35-7.45 (m, 2 H), 6.9-7.05 (m, 4 H), 4.85 (d, 2 H, J = 6.1 Hz, $NHCH_2Ar$), 3.95-4.25 (m, 4 H, CH_2NOH and CH_2OCO), 2.99 (s, 3 H, SO_2CH_3), 2.5-2.8 (m, 3 H, $CHCH_2Ph$), 2.2-2.3 (m, 6 H, 2 x CH_3), 1.20 (s, 9 H, $C(CH_3)_3$)

Example 30. Preparation of N-[2-(4-*tert*-butylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[4-(methylsulfonylamino)benzyl]thiourea compound(40, SU-552)

The mixture of compound 17 and 9 was treated according to the same procedure described in above Example 17 to give white solid of N-[2-(4-*tert*-butylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[4-(methylsulfonylamino)benzyl]thiourea compound 40 (yield : 97%)(*See* Table 3).

melting point : 149-150 °C

^{1}H-NMR($CDCl_3$) δ: 7.79 (bs, 1 H, OH), 7.25-7.32 (m, 4 H), 7.1-7.18 (m, 4 H, Ar), 6.91 (bs, 1 H, $NHSO_2$), 4.75 (d, 2 H, J = 5.5 Hz, $NHCH_2Ar$), 4.29 (dd of AB, 1 H, J = 10.3, 14.5 Hz, CH_2NOH), 4.12 (m, 2 H, CH_2OCO), 3.98 (dd of AB, 1 H, J = 5, 14.5 Hz, CH_2NOH), 2.96 (s, 3 H, SO_2CH_3), 2.69 (d, 2 H, J = 7 Hz, CH_2Ar), 2.59 (bs, 1 H, CH), 1.29 (s, 9 H, $C(CH_3)_3$), 1.16 (s, 9 H, $C(CH_3)_3$)

IR (KBr): 3295, 3186, 2964, 1706, 1529, 1321, 1184, 1147 cm^{-1}

MS *m/z* : 564(MH^+)

Example 31. Preparation of N-[2-(4-*tert*-butylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[3-fluoro-4-(methylsulfonylamino)benzyl]thiourea compound(41)

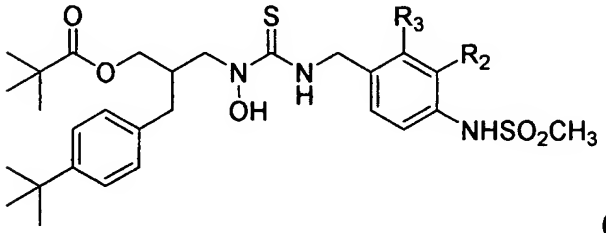
The mixture of compound 19 and 9 was treated according to the same procedure described in above Example 17 to give white solid of N-[2-(4-*tert*-butylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[3-fluoro-4-(methylsulfonylamino)benzyl]thiourea compound 41 (yield : 95%)(*See* Table 3).

melting point : 128-129 °C

^{1}H-NMR($CDCl_3$) δ: 7.83 (bs, 1 H), 7.49 (t, 1 H, J = 8.0 Hz), 7.31 (d, 2 H, J = 8.3 Hz), 7.05-7.2 (m, 3 H), 6.60 (bs, 1 H, $NHSO_2$), 4.79 (m, 2 H, $NHCH_2Ar$), 4.29 (dd, 1 H, CH_2OCO), 4.05-4.20 (m, 2 H, CH_2NOH), 3.97 (dd, 1 H, CH_2OCO), 3.00 (s, 3 H, SO_2CH_3), 2.69 (d, 2 H, J = 7.1 Hz, CH_2Ar), 2.58 (bs, 1 H, CH), 1.29 (s, 9 H, $C(CH_3)_3$), 1.16 (s, 9 H, $C(CH_3)_3$)

IR (KBr): 3244, 2964, 1716, 1509, 1331, 1158 cm^{-1}

MS *m/z* : 582 (MH^+)



(IX)

Table 3

Group	Compound	R_2	R_3	Yield (%)	Spectrum data
IV	40	H	H	97	^{1}H-NMR($CDCl_3$) δ: 7.79 (bs, 1 H, OH), 7.25-7.32 (m, 4 H), 7.1-7.18 (m, 4 H, Ar), 6.91 (bs, 1 H, $NHSO_2$), 4.75 (d, 2 H, J = 5.5 Hz, $NHCH_2Ar$), 4.29 (dd of AB, 1 H, J = 10.3, 14.5 Hz, CH_2NOH), 4.12 (m, 2 H, CH_2OCO), 3.98 (dd of AB, 1 H, J = 5, 14.5 Hz, CH_2NOH), 2.96 (s, 3 H, SO_2CH_3), 2.69 (d, 2 H, J = 7 Hz, CH_2Ar), 2.59 (bs, 1 H, CH), 1.29 (s, 9 H, $C(CH_3)_3$), 1.16 (s, 9 H, $C(CH_3)_3$)

	41	F	H	95	^{1}H-NMR($CDCl_3$) δ: 7.83 (bs, 1 H), 7.49 (t, 1 H, J = 8.0 Hz), 7.31 (d, 2 H, J = 8.3 Hz), 7.05-7.2 (m, 3 H), 6.60 (bs, 1 H, $NHSO_2$), 4.79 (m, 2 H, $NHCH_2Ar$), 4.29 (dd, 1 H, CH_2OCO), 4.05-4.20 (m, 2 H, CH_2NOH), 3.97 (dd, 1 H, CH_2OCO), 3.00 (s, 3 H, SO_2CH_3), 2.69 (d, 2 H, J = 7.1 Hz, CH_2Ar), 2.58 (bs, 1 H, CH), 1.29 (s, 9 H, $C(CH_3)_3$), 1.16 (s, 9 H, $C(CH_3)_3$)

Example 32. Preparation of 4-(methylsulfonylamino)phenyl acetic acid compound(43)

A solution of 4-aminophenylacetic acid (1 g, 6.66 mmol) in THF (10 ㎖) was adjusted to pH 9 with 1 N sodium hydroxide. The mixture was reacted by the dropwise addition of methansulfonyl chloride (0.77 ㎖, 9.99 mmol) in THF (10 ㎖), adjusted to pH 3 with 1 N hydrochloric acid, diluted with distilled water and extracted with ethyl acetate several times. The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by flash column chromatography on Silica gel with EtOAc/hexanes (2:3) solvent mixture as an eluant to give 0.855g of yellow solid of 4-(methylsulfonylamino)phenylacetic acid compound 43 (yield : 56%).

^{1}H-NMR(DMSO-d_6) δ: 9.67 (s, 1 H, COOH), 7.20 (d, 2 H, J = 8.5 Hz, Ar), 7.13 (d, 2 H, J = 8.5 Hz, Ar), 3.50 (s, 2 H, CH_2), 3.95 (s, 3 H, SO_2CH_3)

Example 33. Preparation of pentafluorophenyl 2-[4-(methylsulfonylamino)phenyl] acetate compound(44)

A cooled solution of 0.6707g of pentafluoro phenol (3.3 mmol) and 0.036g of dimethylaminopyridine (0.3 mmol) in dichloromethane (15 ㎖) was reacted by the dropwise addition of 4.5 ㎖ of 1.0M dicyclohexyl carboimide and stirred for 16 hours at room temperature. The reaction mixture was concentrated *in vacuo*, diluted with ether, filtered and the filtrate was concentrated again in *vacuo*. The residue was purified by column chromatography with EtOAc/hexanes (1:10) solvent mixture as an eluant to give 0.592g of white solid of pentafluorophenyl 2-[4-(methylsulfonylamino)phenyl] acetate compound 44 (yield : 50%).

^{1}H-NMR($CDCl_3$) δ: 7.36 (d, 2 H, J = 8.5 Hz, Ar), 7.24 (d, 2 H, J = 8.5 Hz, Ar), 3.96 (s, 2 H, CH_2), 3.03 (s, 3 H, SO_2CH_3).

Example 34. Preparation of N-(4-*tert*-butylbenzyl)-N-hydroxy-[4-(methylsulfonylamino)phenyl] acetamide compound(45)

The mixture of compound 44 and 3 was condensed according to the same procedure described in above Example 33 to give white solid of N-(4-*tert*-butylbenzyl)-N-hydroxy-[4-(methylsulfonylamino)phenyl]acetamide compound 45 (yield : 47%) (*See* Table 4).

melting point : 161-163 °C

^{1}H-NMR(acetone-d_6) δ: 9.02 (bs, 1 H, OH), 8.48 (bs, 1 H, $NHSO_2$), 7.2-7.4 (m, 8 H, Ar), 4.75 (s, 2 H, CH_2NOH), 3.82 (s, 2 H, CH_2CO), 2.95 (s, 3 H, SO_2CH_3), 1.29 (s, 9 H, $C(CH_3)_3$)

IR (KBr): 3350, 1650, 1515, 1338, 1154 cm^{-1}

MS *m/z* : 391 (MH^+)

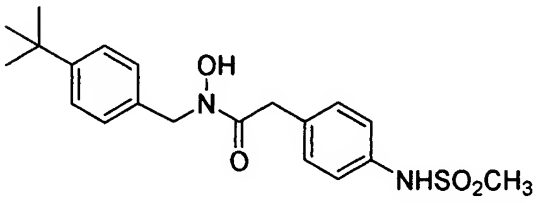


Table 4

Group	Compound	Yield (%)	Spectrum data
IV	45	47	^{1}H-NMR(acetone-d_6) δ: 9.02 (bs, 1 H, OH), 8.48 (bs, 1 H, $NHSO_2$), 7.2-7.4 (m, 8 H, Ar), 4.75 (s, 2 H, CH_2NOH), 3.82 (s, 2 H, CH_2CO), 2.95 (s, 3 H, SO_2CH_3), 1.29 (s, 9 H, $C(CH_3)_3$)

Example 35. Preparation of *tert*-butyl N-[(*tert*-butoxycarbonyl)oxy]-N-(4-nitrobenzyl)carbamate compound(47)

4-nitrobenzyl bromide as a starting material was reacted with *tert*-butyl-N-(*tert*-butoxycarbonyloxy)carbamate under basic condition to give colorless oil of *tert*-butyl N-[(*tert*-butoxycarbonyl)oxy]-N-(4-nitrobenzyl)carbamate compound 47 (yield : 81%).

^{1}H-NMR($CDCl_3$) δ: 8.14 (dt, 2 H, J = 2.2, 8.6 Hz, Ar), 7.48 (d, 2 H, J = 8.6 Hz, Ar), 4.81 (s, 2H, CH_2), 1.44 (bs, 18 H, 2 x $C(CH_3)_3$)

Example 36. Preparation of *tert*-butyl N-[(*tert*-butoxycarbonyl)oxy]-N-(4-nitrobenzyl)carbamate compound(48)

A suspension of compound 47 (6.40 g, 17.3 mmol) and Pd-C (650 mg) in MeOH (100 mℓ) was hydrogenated under a hydrogen balloon for 2 hrs. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in 60ml pyridine. The mixture was treated with methansulfonylchloride (20.1 mℓ, 26.0 mmol) and stirred for 16 hours at room temperature. The reaction mixture was concentrated *in vacuo*, diluted with distilled water, extracted with ethyl acetate several times.

The combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on Silica gel with EtOAc/hexanes (2:3) solvent mixture as an eluant to give 6.56g of viscous syrup of *tert*-butyl N-[(*tert*-butoxycarbonyl)oxy]-N-(4-nitrobenzyl)carbamate compound 48 (yield : 91%).

^{1}H-NMR($CDCl_3$) δ: 7.32 (d, 2 H, J = 8.6 Hz, Ar), 7.20 (dd, 2 H, J = 1.7, 8.6 Hz, Ar), 4.72 (s, 2 H, CH_2), 2.99 (s, 3 H, SO_2CH_3), 1.48 (bs, 18 H, 2 x $C(CH_3)_3$).

Example 37. Preparation of N-[4-(methylsulfonylamino)benzyl]hydroxylamine compound(49)

A cooled solution of the compound 48 (6.56 g, 15.7 mmol) was treated with trifluoroacetic acid (30 mℓ) at 0 °C and stirred for 20 mins at room temperature. The mixture was concentrated *in vacuo* to obtain 5.19g of yellow solid of N-[4-(methylsulfonylamino)benzyl]hydroxylamine 49 (yield : 100%).

^{1}H-NMR(DMSO-d_6) δ: 11.26 (bs, 1 H), 10.8 (bs, 1 H), 9.87 (s, 1 H), 7.34 (d, 2 H, J = 8.5 Hz, Ar), 7.15 (dd, 2 H, J = 8.5 Hz, Ar), 4.19 (s, 2 H, CH_2), 2.94 (s, 3 H, SO_2CH_3).

Example 38. Preparation of benzyl N-(2-fluoro-4-methylphenyl)carbamate compound(51)

A solution of 2-fluoro-4-methylaniline compound 50 (400 mg, 3.2 mmol) in pyridine (4 mℓ) was reacted by dropwise addition of benzylchloroformate (0.68 mℓ, 4.8 mmol) at 0 °C. After being stirred for 20 min at 0 °C, the reaction was stopped by addtion of 0.2 mℓ ethanol. The reaction mixture was diluted with distilled water, filtered. The residue was purified by column chromatography on Silica gel with EtOAc/hexanes (1:10) solvent mixture as an eluant to give 730 mg of pale pink solid of benzyl N-(2-fluoro-4-methylphenyl)carbamate compound 51 (yield : 88%).

melting point : 66 °C

^{1}H-NMR($CDCl_3$) δ: 7.93 (bt, 1 H), 7.3-7.45 (m, 5 H, Ph), 6.86-6.93 (m, 2 H), 6.80 (bs, 1 H, NH), 5.21 (s, 2 H, OCH_2Ph), 2.30 (s, 3 H, CH_3)

Example 39. Preparation of benzyl N-(4-(bromomethyl)-2-fluorophenyl)carbamate compound(52)

A solution of 500 mg of benzyl N-(2-fluoro-4-methylphenyl)carbamate compound 51 in dichloromethane (8 ㎖) was treated with NBS (360 mg, 2.02 mmol) and AIBN as a catalyst. The reaction mixture was refluxed under 300-watt halogen lamp for 150 mins, cooled down at room temperature and dehydrated. The residue was purified by column chromatography on Silica gel with EtOAc/hexanes (1:10) solvent mixture as an eluant to give 268 mg of dark gray solid of N-(4-(bromomethyl)-2-fluorophenyl)carbamate compound 52 (yield : 41%).

melting point : 95-96 °C

^{1}H-NMR ($CDCl_3$) δ: 8.10 (bt, 1 H, J = 8.4 Hz), 7.35-7.45 (m, 5 H, Ph), 7.10-7.16 (m, 2 H), 6.94 (bs, 1 H, NH), 5.22 (s, 2 H, OCH_2Ph), 4.43 (s, 2 H, CH_2Br)

Example 40. Preparation of *tert*-butyl N-[(*tert*-butoxycarbonyl)oxy]-N-{4-[(benzyloxy)carbonylamino]-3-fluorobenzyl}carbamate compound(53)

A solution of *tert*-butyl-N-(*tert*-butoxycarbonyloxy)carbamate (224 mg, 0.96 mmol) in DMF (2 ㎖) was reacted with sodium hydride (38 mg, 0.96 mmol) at 0 °C and stirred for 20 mins at room temperature. The reaction mixture was treated by dropwise addition of benzyl N-[4-(bromomethyl)-2-fluorophenyl]carbamate compound 52 (250 mg, 0.74 mmol) and stirred for 1 hour. After concentrating, residual mixture was purified by column chromatography on Silica gel with EtOAc/hexanes (1:5) solvent mixture as an eluant to give 355 mg of yellow oil of *tert*-butyl N-[(*tert*-butoxycarbonyl)oxy]-N-{4-[(benzyloxy)carbonylamino]-3-fluorobenzyl}carbamate compound 53 (yield : 98%).

^{1}H-NMR($CDCl_3$) δ: 8.06 (bt, 1 H), 7.35-7.45 (m, 5 H, Ph), 7.05-7.12 (m, 2 H), 6.89 (bs, 1 H, NH), 5.22 (s, 2 H, OCH_2Ph), 4.68 (s, 2 H, CH_2NO), 1.48 (s, 9 H, $C(CH_3)_3$), 1.47 (s, 9 H, $C(CH_3)_3$)

Example 41. Preparation of *tert*-butyl N-[(4-amino-3-fluorobenzyl)-N-[(*tert*-butoxycarbonyl)oxy]carbamate compound (54)

A suspension of compound 53 (350 mg, 0.714 mmol) and 10% Pd-C (35 mg) in MeOH (8 ㎖) was hydrogenated under a hydrogen balloon for 2 hrs at room temperature. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was crystallized by hexane to give 232 mg of ivory solid of *tert*-butyl N-[(4-amino-3-fluorobenzyl)-N-[(*tert*-butoxycarbonyl)oxy]carbamate compound 54 (yield : 91%).

melting point : 105-106 °C

^{1}H-NMR($CDCl_3$) δ: 6.99 (dd, 1 H, J = 1.6, 12 Hz), 6.90 (dd, 1 H, J = 1.6, 8.1 Hz), 6.71 (t, 1 H, J = 8.8 Hz), 4.61 (s, 2 H, CH_2NO), 3.70 (bs, 2 H, NH_2), 1.48 (s, 9 H, $C(CH_3)_3$), 1.47 (s, 9 H, $C(CH_3)_3$)

Example 42. Preparation of *tert*-butyl N-[(*tert*-butoxycarbonyl)oxy]-N-[3-fluoro-4-(methylsulfonylamino)benzyl]carbamate compound (55, SU-576)

A cooled solution of compound 54 (210 mg, 0.59 mmol) in pyridine (2 ㎖) was reacted by dropwise addition of methansulfonyl chloride (0.09 ㎖, 1.178 mmol) at 0 °C and stirred for 30 mins at 0 °C. The reaction mixture was purified by column chromatography on Silica gel with EtOAc/hexanes (1:2) solvent mixture as an eluant and crystailized by hexane and diethylester to give 238 mg of *tert*-butyl N-[(*tert*-butoxycarbonyl)oxy]-N-[3-fluoro-4-

(methylsulfonylamino)benzyl]carbamate compound 55 (SU-576) (yield : 93%).

melting point : 112-113 °C

^{1}H-NMR ($CDCl_3$) δ: 7.53(t, 1 H, J = 8.25 Hz), 7.12-7.2(m, 2 H), 6.90(bs, 1 H, NH), 4.73(s, 2 H, CH_2NO), 3.02(s, 3 H, SO_2CH_3), 1.49 s, 18 H)

Example 43. Preparation of N- [3-fluoro-4-(methylsulfonylamino)benzyl] hydroxylamine compound (56)

A cooled solution of compound 55 (225 mg, 0.518 mmol) in dichloromethane (10 ㎖) was reacted with trifluoroacetic acid (2 ㎖) at 0 °C and stirred for 50 mins at room temperature. The reaction mixture was dehydrated below the room temperature, concentrated *in vacuo*. The residue was dissolved in ethyl acetate and washed with saturated sodium bicarbonate several times.

The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give N- [3-fluoro-4-(methylsulfonylamino)benzyl] hydroxylamine compound 56.

^{1}H-NMR($CDCl_3$) δ: 7.56 (m, 1 H), 7.1-7.3 (m, 2 H), 7.02 (bs, 1 H, $NHSO_2$), 4.85 (s, 2 H, CH_2NOH), 2.94 (s, 3 H, SO_2CH_3)

Example 44. Preparation of 4-(*tert*-butylbenzyl)isothiocyanate compound (57)

A cooled solution of 4-*tert*-butylbenzylamine (1 g, 6.13 mmol) and triethylamine (1.29 ㎖, 9.20 mmol) in dichloromethane (20 ㎖) was reacted with 1,1-thio-di-2-pyridone(1.42g, 6.13 mmol) at 0 °C, stirred for 20 mins at room temperature and concentrated *in vacuo*. The residue was purified by column chromatography on Silica gel with EtOAc/hexanes (1:10) solvent

mixture as an eluant to give 0.755 g of white solid of 4-(*tert*-butylbenzyl)isothiocyanate compound 57 (yield : 60%).

melting point : 47.3 °C

^{1}H-NMR($CDCl_3$) δ: 7.40 (dt, 2 H, J = 2.2, 8.6 Hz, Ar), 7.24 (d, 2 H, J = 8.6 Hz, Ar), 4.67 (s, 2 H, CH_2), 1.32 (s, 9 H, $C(CH_3)_3$)

Example 45. Preparation of 4-(*tert*-butylbenzyl)isothiocyanate compound (58)

A solution of 4-*tert*-butylbenzylamine (1 g, 6.13 mmol) in toluene (10 mℓ) was reacted with triphosgen (2.48 g, 9.20 mmol). The reaction mixture was refluxed at 100 °C for 20 mins and concentrated *in vacuo*. The residue was purified by column chromatography on Silica gel with EtOAc/hexanes (1:10) solvent mixture as an eluant to give 0.859 g of colorless oil of 4-(*tert*-butylbenzyl)isothiocyanate compound 58 (yield : 74 %).

^{1}H-NMR($CDCl_3$) δ: 7.39 (dt, 2 H, J = 2.2, 8.6 Hz, Ar), 7.23 (d, 2 H, J = 8.6 Hz, Ar), 4.43 (s, 2 H, CH_2), 1.31 (s, 9 H, $C(CH_3)_3$)

Example 46. Preparation of pentafluorophenyl 2-(4-*tert*-butylphenyl)acetate compound (59)

A cooled solution of 4-*tert*-butylphenyl acetic acid (1 g, 5.20 mmol), pentafluorophenol (1.15 g, 6.24 mmol) and dimethylaminopyridine in dichloromethane (30 mℓ) was reacted with 1.0 M dicyclohexylcarbodiimide (6.24 mℓ, 6.24 mmol) at 0°C. And the reaction mixture was stirred for 16 hours at room temperature, concentrated *in vacuo*, diluted with ether and filtered. The filtrate was concentrated again *in vacuo* and purified by column chromatography on Silica

gel with EtOAc/hexanes (1:10) solvent mixture as an eluant to give 1.86 g of colorless oil of pentafluorophenyl 2-(4-*tert*-butylphenyl)acetate compound 59 (yield : 100 %).

^{1}H-NMR($CDCl_3$) δ: 7.40 (dt, 2 H, J = 2.2, 8.3 Hz, Ar), 7.28 (d, 2 H, J = 8.3 Hz, Ar), 3.94 (s, 2 H, CH_2), 1.32 (s, 9 H, $C(CH_3)_3$)

Example 47. Preparation of N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[4-(methylsulfonylamino)benzyl]thiourea compound (60)

N-[4-(methylsulfonylamino)benzyl]hydroxylamine compound 49 (165 mg, 0.5 mmol) and isopropylethylamine (0.13 ㎖, 0.75 mmol) in DMF 3 ㎖ was stirred for 1 hour at room temperature. The mixture was further added with above compound 57 (0.5 mmol), stirred for 20 hour at room temperature, diluted with H_2O and extracted with ethylacetate several times. The combined organic layers were washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo.* The residue was purified by column chromatography with EtOAc/hexanes (2:1) solvent mixture as an eluant to give white solid of N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[4-(methylsulfonylamino)benzyl]thiourea compound 60 (yield : 90%) (*See* Table 5).

melting point : 124 °C

^{1}H-NMR(acetone-d_6) δ: 8.77 (bs, 1 H, N-OH), 8.22 (t, 1 H, J = 6.0 Hz, NHCS), 7.25-7.45 (m, 8 H), 5.34 (s, 2 H, $HONCH_2Ar$), 4.84 (d, 2 H, J = 6.0 Hz, $ArCH_2NH$), 2.97 (s, 3 H, SO_2CH_3), 1.29 (s, 9 H, $C(CH_3)_3$)

MS *m/z* : 422 (MH^+)

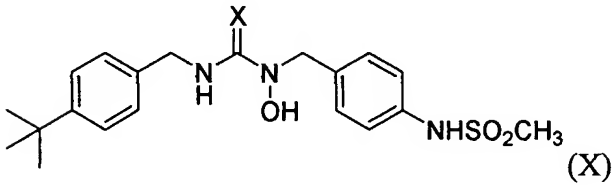
Example 48. Preparation of N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[4-(methylsulfonylamino)benzyl]urea compound (62)

N-[4-(methylsulfonylamino)benzyl]hydroxylamine compound 49 (165 mg, 0.5 mmol) and isopropylethylamine (0.13 ㎖, 0.75 mmol) in DMF 3 ㎖ was stirred for 1 hour at room temperature. The mixture was further added with above compound 58 (0.5 mmol), stirred for 20 hour at room temperature, diluted with H_2O and extracted with ethylacetate several times. The combined organic layers were washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo.* The residue was purified by column chromatography with EtOAc/hexanes (2:1) solvent mixture as an eluant to give white solid of N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[4-(methylsulfonylamino)benzyl]urea compound 62 (yield : 74%) (*See* Table 5).

melting point : 125 °C

^{1}H-NMR ($CDCl_3$) δ 7.32 (d, 2 H, J = 8.3 Hz), 7.27 (d, 2 H, J = 8.3 Hz), 7.18 (d, 2 H, J = 8.3 Hz), 7.10 (d, 2 H, J = 8.3 Hz), 6.76 (bs, 1 H, NH), 6.69 (bs, 1 H, OH), 6.29 (t, 1 H, J = 5.8 Hz, NH), 4.59 (s, 2 H, $HONCH_2Ar$), 4.36 (d, 2 H, J = 5.8 Hz, $ArCH_2NH$), 2.96 (s, 3 H, SO_2CH_3), 1.29 (s, 9 H, $C(CH_3)_3$)

MS *m/z* :406 (MH^+)



(X)

Table 5

Group	Compound	X	Yield (%)	Spectrum data
V	60	S	80	^{1}H-NMR(acetone-d_6) δ: 8.77 (bs, 1 H, N-OH), 8.22 (t, 1 H, *J* = 6.0 Hz, NHCS), 7.25-7.45 (m, 8 H), 5.34 (s, 2 H, $HONCH_2Ar$), 4.84 (d, 2 H, *J* = 6.0 Hz, $ArCH_2NH$), 2.97 (s, 3 H, SO_2CH_3), 1.29 (s, 9 H, $C(CH_3)_3$)
	62	O	74	^{1}H-NMR ($CDCl_3$) δ 7.32 (d, 2 H, *J* = 8.3 Hz), 7.27 (d, 2 H, *J* = 8.3 Hz), 7.18 (d, 2 H, *J* = 8.3 Hz), 7.10 (d, 2 H, *J* = 8.3 Hz), 6.76 (bs, 1 H, NH), 6.69 (bs, 1 H, OH), 6.29 (t, 1 H, *J* = 5.8 Hz, NH), 4.59 (s, 2 H, $HONCH_2Ar$), 4.36 (d, 2 H, *J* = 5.8 Hz, $ArCH_2NH$), 2.96 (s, 3 H, SO_2CH_3), 1.29 (s, 9 H, $C(CH_3)_3$)

Example 49. Preparation of N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[4-(methylsulfonylamino)benzyl]thiourea compound (61)

N-[4-(methylsulfonylamino)benzyl]hydroxylamine compound 49 (165 mg, 0.5 mmol) and isopropylethylamine (0.13 mℓ, 0.75 mmol) in DMF 3 mℓ was stirred for 1 hour at room temperature. The mixture was further added with above compound 26 (0.5 mmol), stirred for 20 hour at room temperature, diluted with H_2O and extracted with ethylacetate several times. The

combined organic layers were washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo.* The residue was purified by column chromatography with EtOAc/hexanes (2:1) solvent mixture as an eluant to give white solid of N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)-N-hydroxy-N-[4-(methylsulfonylamino)benzyl] thiourea compound 61 (yield : 35%) (*See* Table 6).

melting point : 49 °C

^{1}H-NMR($CDCl_3$) δ: 7.37 (d, 2 H, J = 7.6 Hz), 7.14 (d, 2 H, J = 7.6 Hz), 6.88-7.1 (m, 3 H, Ph and NH), 6.6-6.7 (bs, 2 H, NH), 5.24 (m, 2 H, $HONHCH_2Ar$), 4.12 (m, 1 H, CH_2OCO), 3.86 (m, 1 H, CH_2OCO), 3.73 (m, 1 H, CH_2NH), 3.50 (m, 1 H, CH_2NH), 2.97 (s, 3 H, SO_2CH_3), 2.6-2.75 (m, 2 H, $CHCH_2Ar$), 2.38 (m, 1 H, $CHCH_2Ar$), 2.21-2.23 (d, 6 H, 2 x CH_3), 1.23 (s, 9 H, $C(CH_3)_3$)

IR (KBr): 3244, 1715, 1514, 1457, 1398, 1329, 1286, 1154 cm^{-1}

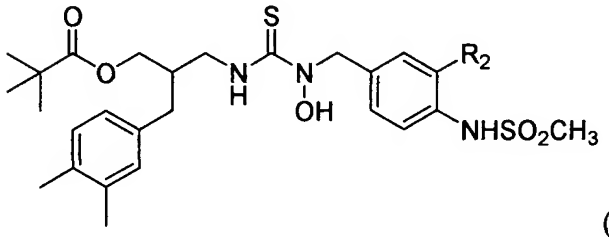
Mass *m/z* : 536 (MH^+)

Example 50. Preparation of N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[3-fluoro-4-(methylsulfonylamino)benzyl]thiourea compound (64)

N-[3-fluoro-4-(methylsulfonylamino)benzyl]hydroxylamine compound 56 (165 mg, 0.5 mmol) and isopropylethylamine (0.13 ㎖, 0.75 mmol) in DMF 3 ㎖ was stirred for 1 hour at room temperature. The mixture was further added with above compound 26 (0.5 mmol), stirred for 20 hour at room temperature, diluted with H_2O and extracted with ethylacetate several times. The combined organic layers were washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo.* The residue was purified by column chromatography with EtOAc/hexanes (2:1) solvent mixture as an eluant to give colorless oil of N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[3-fluoro-4-(methylsulfonylamino)benzyl]thiourea compound 64 (yield : 41 %) (*See* Table 6).

^{1}H-NMR($CDCl_3$) δ: 7.45 (t, 1 H, J = 8.25 Hz), 7.31 (m, 1 H), 7.12-7.25 (m, 2 H), 6.9-7.05 (m, 2 H), 6.70 (bs, 1 H, NH), 5.20 (m, 2 H, CH_2NOH), 4.12 (m, 1 H, CH_2OCO), 3.86 (m, 1 H, CH_2OCO), 3.75 (m, 1 H, CH_2NH), 3.48 (m, 1 H, CH_2NH), 3.00 (s, 3 H, SO_2CH_3), 2.6-2.8 (m, 2 H, CH_2Ar), 2.36 (m, 1 H, CH), 2.2-2.3 (m, 6 H, 2 x CH_3), 1.23 (s, 9 H, $C(CH_3)_3$), 1.22 (s, 9 H, $C(CH_3)_3$)

MS m/z : 554 (MH^+)



(XI)

Table 6

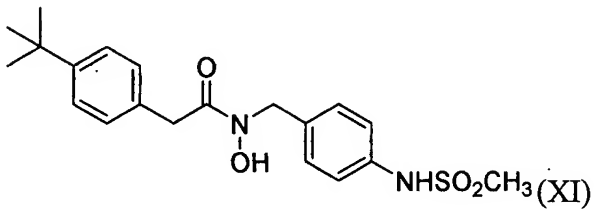
Group	Compound	R_2	Yield (%)	Spectrum data
V	61	H	74	^{1}H-NMR($CDCl_3$) δ: 7.37 (d, 2 H, J = 7.6 Hz), 7.14 (d, 2 H, J = 7.6 Hz), 6.88-7.1 (m, 3 H, Ph and NH), 6.6-6.7 (bs, 2 H, NH), 5.24 (m, 2 H, $HONHCH_2Ar$), 4.12 (m, 1 H, CH_2OCO), 3.86 (m, 1 H, CH_2OCO), 3.73 (m, 1 H, CH_2NH), 3.50 (m, 1 H, CH_2NH), 2.97 (s, 3 H, SO_2CH_3), 2.6-2.75 (m, 2 H, $CHCH_2Ar$), 2.38 (m, 1 H, $CHCH_2Ar$), 2.21-2.23 (d, 6 H, 2 x CH_3), 1.23 (s, 9 H, $C(CH_3)_3$)
	64	F	41	^{1}H-NMR($CDCl_3$) δ: 7.45 (t, 1 H, J = 8.25 Hz), 7.31 (m, 1 H), 7.12-7.25 (m, 2 H), 6.9-7.05 (m, 2 H), 6.70 (bs, 1 H, NH), 5.20 (m, 2 H, CH_2NOH), 4.12 (m, 1 H, CH_2OCO), 3.86 (m, 1 H, CH_2OCO), 3.75 (m, 1 H, CH_2NH), 3.48 (m, 1 H, CH_2NH), 3.00 (s, 3 H, SO_2CH_3), 2.6-2.8 (m, 2 H, CH_2Ar), 2.36 (m, 1 H, CH), 2.2-2.3 (m, 6 H, 2 x CH_3), 1.23 (s, 9 H, $C(CH_3)_3$), 1.22 (s, 9 H, $C(CH_3)_3$)

Example 51. Preparation of N-hydroxy-N-[4-(methylsulfonylamino)benzyl]-2-(4-*tert*-butylphenyl)acetamide compound (63)

N-[4-(methylsulfonylamino)benzyl]hydroxylamine compound 49 (165 mg, 0.5 mmol) and isopropylethylamine (0.13 ㎖, 0.75 mmol) in DMF 3 ㎖ was stirred for 1 hour at room temperature. The mixture was further added with above compound 59 (0.5 mmol), stirred for 20 hours at room temperature, diluted with H_2O and extracted with ethylacetate several times. The combined organic layers were washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo.* The residue was purified by column chromatography with EtOAc/hexanes (2:1) solvent mixture as an eluant to give white solid of N-hydroxy-N-[4-(methylsulfonylamino)benzyl]-2-(4-*tert*-butylphenyl)acetamide compound 63 (yield : 38 %) (*See* Table 7).

^{1}H-NMR(acetone-d_6) δ 7.32 (d, 2 H, J = 8.3 Hz), 7.25 (s, 4 H), 7.21 (d, 2 H, J = 8.3 Hz), 4.76 (s, 2 H, $HONCH_2Ar$), 3.80 (s, 2 H, $ArCH_2CO$), 2.96 (s, 3 H, SO_2CH_3), 1.28 (s, 9 H, $C(CH_3)_3$)

MS *m/z* : 391 (MH^+)



(XI)

Table 7

Group	Compound	Yield (%)	Spectrum data
VI	63	38	^{1}H-NMR(acetone-d_6) δ 7.32 (d, 2 H, J = 8.3 Hz), 7.25 (s, 4 H), 7.21 (d, 2 H, J = 8.3 Hz), 4.76 (s, 2 H, $HONCH_2Ar$), 3.80 (s, 2 H, $ArCH_2CO$), 2.96 (s, 3 H, SO_2CH_3), 1.28 (s, 9 H, $C(CH_3)_3$)

Reference Example 1. Vanilloid receptor binding affinity assay

The binding affinity activity of the target compounds for vanilloid receptor-1 was measured by an *in vitro* receptor binding affinity assay. In the receptor binding assay, the compounds were evaluated for their ability to displace bound [^{3}H]RTX from the receptor. The results are expressed in terms of *Ki* values (mean ± SEM, 3 experiments) which represent the concentration of the non-radioactive ligand that displaces half of the bound labeled RTX.

Cell Culture Preparation

The VR receptor binding affinity activity of the inventive compounds was measured by using Chinese Hamster Ovary (CHO, ATCC, No. CCL-61) cell whose cDNA of VR1(pUHG102 VR1 plasmid) was transfected, which can control the expression of VR1 according to the presence of tetracycline and Tetracycline on/off system (pTet off regulatory plasmid, Clontech. Inc., USA) that the expression of VR1 is induced by removing tetracycline from the medium. CHO cells were cultured in the medium containing 1㎍/㎖ of tetracycline (T-7660, Sigma-

Aldrich. Co., USA) and 10㎍/㎖ of puromycin for stabilizing the cell line. The cells were cultured after removing tetracycline prior to 48 hours. The tetracycline free culture medium was seeded at the bottom of T75 flask, incubated to the extent that its density reaches at 90%, and washed once with PBS buffer solution. The cells were collected by using saline solution containing 5mM EDTA and subjected to centrifugation slightly to obtain precipitates, further, which had been kept at the temperature of -20 °C before use.

Resiniferatoxin(RTX) competition binding assay.

[^{3}H] RTX binding assay of present invention was performed with the procedure described in the literature (Szallasi et al.; *Pharmacol. Exp. Ther.*, 262, pp883-888, 1992). Experiments were designed to assess inhibition of specific [^{3}H]RTX binding to membranes by non-radioactive compounds. The binding assay mixture containing [^{3}H]RTX (80 pM), various concentrations of competitive binding substances, 0.25mg/㎖ of BSA(Cohn fraction V), $5x10^4$ ~ $5x10^5$ numbers of VR1 and the expression cell, was admixed with saline solution containing 450 ㎕ of Ca^{2+} and Mg^{2+} and 0.25㎎/㎕ of BSA. Non-specific binding assay was measured after mixing 100nM of non-radioactive RTX thereto. The reaction mixture was treated for 60 min at 37 °C and the reaction was quenched by cooling over ice. RTX bound to the membrane of VR1 was subjected to centrifugation with maximum velocity for 15 minutes to precipitate its membrane residue, which results in separating from non-binding RTX. The tips of tube containing above precipitate was cut off and the amount of bound radioisotope was determined by scintillation counter (LS6500, Beckman-Coulter, USA). The measurement of binding was determined in triplicate in each experiment, and each experiment was repeated at least two times.

Binding data were analyzed by fitting to the Hill equation and the *Ki* (equilibrium binding parameter) index, the *Bmax* (maximum binding parameter) index, and the cooperativity index etc., were determined by using origin 6.0 program (Origin, MicroCal Co., USA).

The preparation of Sample

An initial compound was dissolved in DMSO(dimethyl sulfoxide) and diluted with saline solution containing Ca^{2+} and Mg^{2+}, and 0.25㎎/㎕ of BSA.

Experimental Example 1: ^{45}Ca Influx test

The ^{45}Ca Influx test by using CHO cells expressing VR1 was performed by the procedure described in the literature (Lee, J. W., *Bioorganic & Medicinal Chemistry*, pp1713-1720, 2001).

The ^{45}Ca Influx test by using CHO cells of the inventive compounds was measured by using Chinese Hamster Ovary (CHO, ATCC, No. CCL-61) cell whose cDNA of VR1(pUHG102 VR1 plasmid) was transfected, which can control the expression of VR1 according to the presence of tetracycline and Tetracycline on/off system (pTet off regulatory plasmid, Clontech. Inc., USA) that the expression of VR1 is induced by removing tetracycline from the medium. The CHO cells were poured onto 24 well plates to the extent that its density reaches at 30% and incubated for 24 hours at 37 °C. The culture medium was exchanged to tetracycline free medium to induce the expression of VR1 and tested after 36 hours.

In radioactive ^{45}Ca uptake experiment, The cells were incubated in 500 ㎕ of DMEM medium (Dulbecco's modified Eagles medium: Gibco-BRL, 31600-083) containing free of serum and 1.8mM $CaCl_2$ for 10 minutes at 37 °C. Together with 0.25 ㎎/㎖ BSA (Sigma A2153, USA), 1 Ci/㎖ ^{45}Ca(5-30 Ci/g used, ICN. Co., 62005 RT, U.S.A.), the test samples with

increasing concentrations were added to each well. At the quenching moment of the incubation with ^{45}Ca, the cultured cells were removed from the medium, washed three times with cool PBS buffer solution containing 1.8mM $CaCl_2$ and 400 $\mu\ell$ of RIPA buffer solution (50mM Tris pH 7.4; 150mM sodium chloride; 0.1% SDS; 1% sodium deoxycholate), was added in each well to homogenize the cells. The plates were stirred for 20 minutes slowly and 300 $\mu\ell$ of cell lysate was transferred to scintillation vials from each wells. The radioactivity was determined by scintillation counter.

The data were assessed by determining four wells per each data point in each experiment and analyzed in computer by being transformed into Hill equation. The experiments were determined in triplicate in each sample comprising inventive compounds and control groups.

In order to determine the antagonistic activity, $^{45}Ca^{2+}$-uptake stimulating-mixture was added with 50nM capsaicin and the antagonistic activity was determined by the method for the agonistic activity. In case that 10μM a certain compound cannot change the capsaicin-inducing activity, the compound shall be regarded as an agonist.

he result of the vanilloid receptor affinity and Ca uptake test of each compound was shown in Table 8.

Table 8

Compound	Code	K*i* (nM) (VR1/CHO)	EC_{50} (nM) (VR1/CHO)	IC_{50} (nM) (VR1/CHO)
Capsazepine		1350 (± 50)	NE	520 (± 12)
28	JYL-1627	1092 (± 145)	NE	470.2 (± 197.8)
29	MY-594	926 (± 74)	2008 (± 198)	NE
30	SU-190	802 (±187)	>7062	NE
31	MY-546	1308.3 (±209.8)	NE	579 (± 42.5)
32	MY-570	1328.4 (± 311.1)	NE	635 (± 51.8)
33	SU-308	1920.8 (± 333.7)	12340 (± 2922)	NE
34	SU-306	2271.6 (± 731.9)	NE	NE
35	SU-66	1041.8 (± 72.8)	1233	212.5 (± 85.3)
36	MY-650	396 (± 62)	809 (± 126)	NE
37	SU-154	211.6 (± 39.6)	NE	93.67 (± 14)
38	SU-288	623.5 (±152.3)	1352 (± 136)	NE
39	SU-276	220.6 (± 54.5)	NE	757.4 (± 65)
40	SU-552	535.6 (± 89.1)	weak	NE
41	SU-530	404.8 (± 15.2)	Weak	Weak
45	JYL-1635	6375.3 (± 3059)	3504 (± 1387)	6589 (± 1986)

60	JYL-1371	4257 (± 372)	NE	465 (± 103)
61	LJO-310	481.1 (± 66.9)	Weak	Weak
62	JYL-1453	3495 (± 621)	1055.4 (± 35.4)	NE
63	JYL-1455	5309 (± 725)	1963 (± 402)	NE
64	SU-578	545.8 (± 52.7)	Weak	NE

Experimental Example 3. Acetic acid-induced writhing test

The acetic acid-induced writhing test for testing the analgesic activity of inventive compounds prepared from above Examples was performed by the procedure described in the literature (Lee, J. W., *Bioorganic & Medicinal Chemistry*, pp1713-1720, 2001).

Male ICR mice having its mean body weight of 25g(CD-1; Biogenomics Co. Korea) were reared in lighting controlled environment (12 hrs on/12 hrs off) maintaining with temperatures at 22 ± 2°C and humidity at 50 ± 5% and allowed to eat a diet and to drink tap water *ad lib.*

Mice were fasted overnight prior to testing and adopted to the environment.

0.3 ㎖ of acetic acid solution (1.2 %) was administrated in the mice intraperitoneally and then the mice were put into the transparent acryl box (15 × 15 × 15 cm). 5 minutes later, the number of abdominal constrictions was counted for 20 minutes. Each group consisting of ten mice was pretreated with test compounds or solvent (0.2 ㎖, i.p.) 30 mins before the injection of acetic acid. Test compounds were dissolved in the mixture of ethanol/Tween-80/saline (10/10/80) or cremophor EL/DMSO/d-water (10/10/80).

Analgesic activity of each drug was determined at several different concentrations. The index of analgesic activity (eff) was defined as below Empirical formula 1.

[Empirical formula 1]

Analgesic activity (eff) = 100 – {(No. of abdominal constriction of test group/ No. of abdominal constriction of control group) ×100}

Analgesic activity was expressed as the reduction in the number of abdominal constrictions, of control animals (vehicle-pretreated mice) and animals pretreated with test compounds. ED_{50}, the concentration of the test group to reduce 50% of the number of writhes and the result was shown in Table 9.

Table 9

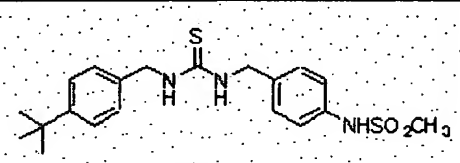
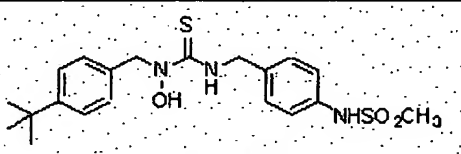
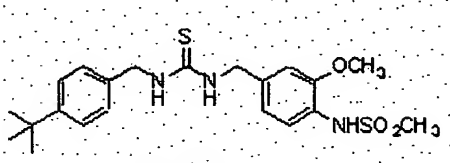
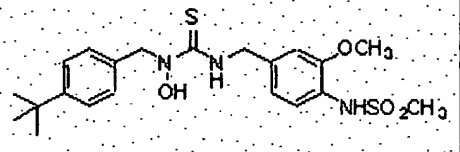
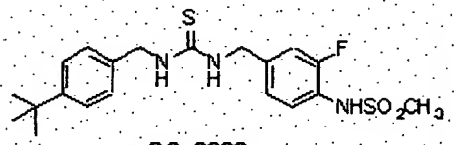
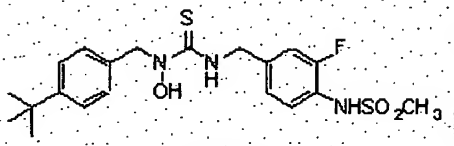
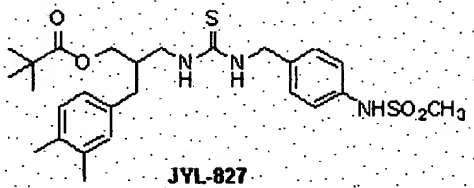
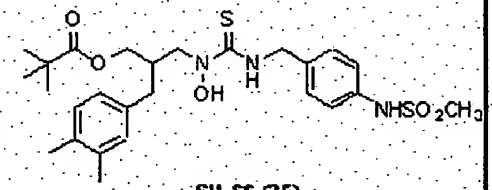
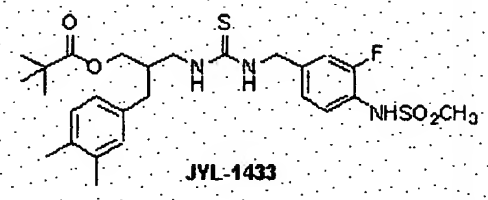
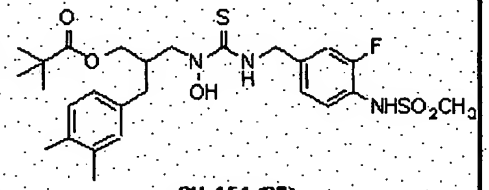
Thiourea	ED_{50} (μg/kg)	N-hydroxy thiourea	ED_{50} (μg/kg)
KJM-429	1.410 (± 320)	28 (JYL-1627)	1.560 (± 270)
JYL-511	0.022 (± 0.118)	29 (MY-594)	0.103 (± 0.061)
SC-0030	1.257 (± 0.0074)	30 (SU-190)	1.072 (± 0.151)
JYL-827	2.620 (± 2.380)	35 (SU-66)	2.600 (± 1.100)
JYL-1433	7.429 (± 8.4)	37 (SU-154)	0.065 (± 0.056)
Ref. Ketorolac ED_{50}(μg/kg) = 2820			

Comparing with the activity of thiourea compound JYL-827 and 1433 disclosed in Korean Patent application No. 2001-50093, the inventive compounds 35 (SU-66) and 37 (SU-154) showed stronger analgesic effect.

Table 10 shows the order of 37(SU-154) > JYL-1433, 35 (SU-66) > JYL-827 in analgesic effect. Especially, compound 37(SU-154) in present invention exhibited 43,000-fold stronger effect than that of Ketorolac, one of the most analgesic compounds in prior art (*See* Table 10 and Fig. 1).

The test results demonstrated that analgesic effect of the compounds used in this experiment is potent, and in particular, it is significant to clarify that vanilloid receptor antagonist can exhibit such potent analgesic effect, and the result suggests that vanilloid receptor antagonist has potential as an analgesic agent.

Table 10

THIOUREA	N-HYDROXY THIOUREA
 KJM-429	 JYL-1627 (28)
 JYL-1511	 MY-594 (29)
 SC-0030	 SU-190 (30)
 JYL-827	 SU-66 (35)
 JYL-1433	 SU-154 (37)

Experimental Example 4: Toxicity test

The acute toxicity tests on ICR mice (mean body weight 25 ± 5g) and Sprague-Dawley rats (235 ± 10g) were performed using the compounds 35 and 37. Each group consisting of 3 mice or rats was administrated intraperitoneally with 20 mg/kg, 10 mg/kg and 1 mg/kg of test compounds or solvents (0.2 mℓ, i.p.), respectively and observed for 24 hrs.

There were no treatment-related effects on mortality, clinical signs, body weight changes and gross findings in any group or either gender. These results suggested that the compounds prepared in the present invention were potent and safe.

Hereinafter, the formulating methods and kinds of excipients will be described, but the present invention is not limited to them. The representative preparation examples were described as follows.

Preparation of powder

Compound 35	500mg
Corn Starch	100mg
Lactose	100mg
Talc	10mg

Powder preparation was prepared by mixing above components and filling sealed package.

Preparation of tablet

Compound 37	100mg
Corn Starch	100mg
Lactose	100mg
Magnesium Stearate	2mg

Tablet preparation was prepared by mixing above components and entabletting.

Preparation of capsule

Compound 35	50mg
Lactose	50mg
Magnesium Stearate	1mg

Tablet preparation was prepared by mixing above components and filling gelatin capsule by conventional gelatin preparation method.

Preparation of injection

Compound 37	100mg
Distilled water for injection	optimum amount
PH controller	optimum amount

Injection preparation was prepared by dissolving active component, controlling pH to about 7.5 and then filling all the components in 2 ㎖ ample and sterilizing by conventional injection preparation method.

Preparation of liquid

Compound 35	1 g
Sugar	10 g
Citric acid	0.05~0.3%
Vitamin C	0.1~1%
Lemon flavor	optimum amount
Distilled water	optimum amount

Liquid preparation was prepared by dissolving active component, adding lemon flavor and distilled water and then filling all the components in 100 ㎖ brown bottle and sterilizing by conventional liquid preparation method.

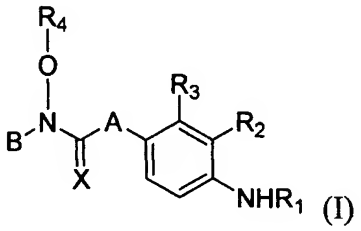
The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the present invention, and all such modifications as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

Industrial Applicability

The novel N-hydroxy thiourea, urea and amide derivatives compounds and the phamaceutical composition comprising same according to the present invention act as vanilloid receptor-1 antagonists and analgesics so the inventive compounds are useful in the prevention, alleviation or treatment of pain, acute pain, chronic pain, neuropathic pain, post-operative pain, migraine, arthralgia, neuropathies, nerve injury, diabetic neuropathy, neurodegeneration, neurotic skin disorder, stroke, urinary bladder hypersensitiveness, irritable bowel syndrome, a respiratory disorder such as asthma or chronic obstructive pulmonary disease, irritation of skin, eye or mucous membrane, fervescence, stomach-duodenal ulcer, inflammatory bowel disease, inflammatory disease or urgent urinary incontinence, etc.

CLAIMS

1. A compound represented by the following general formula (I), the pharmaceutically acceptable salt or the isomer thereof:

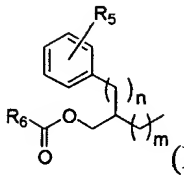


(I)

wherein

X is an oxygen or sulfur atom;

A is an aminomethylene or methylene group;

B is a 4-*tert*-butylbenzyl, a 3,4-dimethylphenylpropyl, an oleyl or 

(I-1) group wherein m is integer of 0 or 1 and n is 1 or 2;

R_1 is a halogen-substituted or unsubstituted lower alkylsulfone having 1 to 5 carbon atoms, arylsulfone or a lower alkylcarbonyl group having 1 to 5 carbon atoms;

R_2 is a hydrogen atom, a methoxy group or halogen atom;

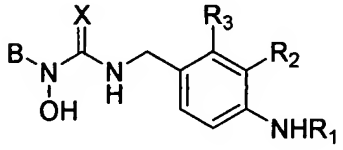
R_3 is a hydrogen atom, a methoxy group or halogen atom;

R_4 is a hydrogen atom or a lower alkyl group having 1 to 5 carbon atoms;

R_5 is a hydrogen atom or a lower alkyl group having 1 to 5 carbon atoms;

R_6 is a lower alkyl group having 1 to 5 carbon atoms or a phenyl group.

2. The compound according to claim 1 represented by the following general formula (III), the pharmaceutically acceptable salt or the isomer thereof:



(III)

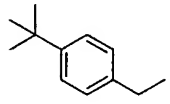
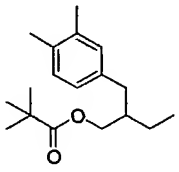
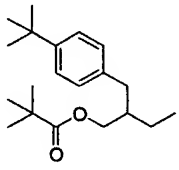
wherein

X is an oxygen atom or a sulfur atom;

R_1 is a halogen-substituted or unsubstituted lower alkylsulfone having 1 to 5 carbon atoms, arylsulfone or a lower alkylcarbonyl group having 1 to 5 carbon atoms;

R_2 is a hydrogen atom, a methoxyl group or a halogen atom;

R_3 is a hydrogen atom or a halogen atom;

B is  ,  or  group.

3. The compound according to claim 2 wherein said compound is at least one selected from the group consisting of;

N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[4-(methylsulfonylamino)benzyl]thiourea,

N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[3-methoxy-4-(methylsulfonylamino) benzyl]thiourea,

N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[3-fluoro-4-(methylsulfonylamino)benzyl] thiourea,

N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[3-chloro-4-(methylsulfonylamino)benzyl] thiourea,

N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[4-(methylsulfonylamino)-3-nitrobenzyl] thiourea,

N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[2-fluoro-4-(methylsulfonylamino)benzyl] thiourea,

N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[2-chloro-4-(methylsulfonylamino)benzyl] thiourea,

N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[4-(methylsulfonyl amino)benzyl] thiourea,

N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[3-methoxy-4-(methylsulfonylamino)benzyl] thiourea,

N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[3-fluoro-4-(methylsulfonylamino)benzyl] thiourea,

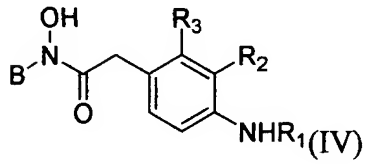
N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[2-fluoro-4-(methylsulfonylamino)benzyl] thiourea,

N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[2-chloro-4-(methylsulfonylamino)benzyl] thiourea,

N-[2-(4-*tert*-butylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[4-(methylsulfonyl amino)benzyl] thiourea, and

N-[2-(4-*tert*-butylbenzyl)-3-(pivaloyloxy)propyl]-N-hydroxy-N-[3-fluoro-4-(methylsulfonylamino)benzyl] thiourea.

4. The compound according to claim 1 represented by the following general formula (IV), the pharmaceutically acceptable salt or the isomer thereof:



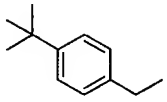
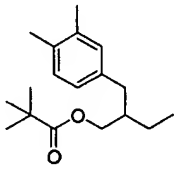
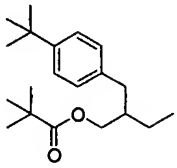
(IV)

wherein

R_1 is a halogen-substituted or unsubstituted lower alkylsulfone having 1 to 5 carbon atoms, arylsulfone or a lower alkylcarbonyl group having 1 to 5 carbon atoms;

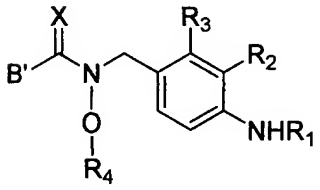
R_2 is a hydrogen atom, a methoxyl group or a halogen atom;

R_3 is a hydrogen atom or a halogen atom;

B is  ,  or  group.

5. The compound according to claim 4 wherein said compound is N-(4-*tert*-butylbenzyl)-N-hydroxy-[4-(methylsulfonylamino)phenyl] acetamide.

6. A compound represented by general formula (II), the pharmaceutically acceptable salt or the isomer thereof:

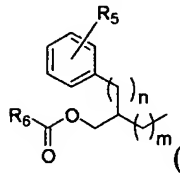

(II)

wherein

X is an oxygen or sulfur atom;

B' is B or a secondary amine substituted with B,

wherein B is a 4-*tert*-butylbenzyl, a 3,4-dimethylphenylpropyl, an oleyl or


(II-1) group, wherein m is integer of 0 or 1 and n is 1 or 2;

R_1 is a halogen-substituted or unsubstituted lower alkylsulfone having 1 to 5 carbon atoms, arylsulfonyl group or lower alkylcarbonyl group having 1 to 5 carbon atoms;

R_2 is a hydrogen atom, a methoxy group or halogen atom;

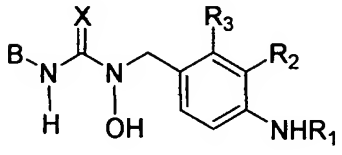
R_3 is a hydrogen atom, a methoxy group or halogen atom;

R_4 is a hydrogen atom or a lower alkyl group having 1 to 5 carbon atoms;

R_5 is a hydrogen atom or a lower alkyl group having 1 to 5 carbon atoms;

R_6 is a lower alkyl group having 1 to 5 carbon atoms or a phenyl group.

7. The compound according to claim 6 represented by general formula (V), the pharmaceutically acceptable salt or the isomer thereof:



(V)

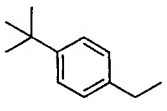
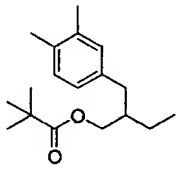
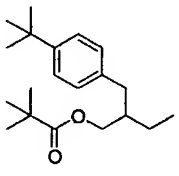
wherein

X is an oxygen atom or a sulfur atom;

R_1 is a halogen-substituted or unsubstituted lower alkylsulfone having 1 to 5 carbon atoms, arylsulfonyl group or lower alkylcarbonyl group having 1 to 5 carbon atoms;

R_2 is a hydrogen atom or a halogen atom;

R_3 is a hydrogen atom;

B is  ,  or  group.

8. The compound according to claim 7 wherein said compound is at least one selected from the group consisting of;

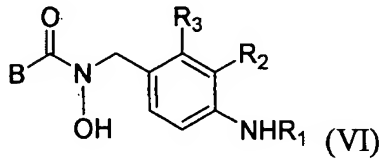
N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[4-(methylsulfonylamino)benzyl]thiourea;

N-[2-(3,4-dimethylbenzyl)-3(pivaloyloxy)propyl]-N-hydroxy-N-[4-(methylsulfonyl amino)benzyl]thiourea,

N-(4-*tert*-butylbenzyl)-N-hydroxy-N-[4-(methylsulfonylamino)benzyl]urea,

N-[2-(3,4-dimethylbenzyl)-3(pivaloyloxy)propyl]-N-hydroxy-N-[3-fluoro-4-(methylsulfonylamino)benzyl]thiourea.

9. The compound according to claim 6 represented by general formula (VI), the pharmaceutically acceptable salt or the isomer thereof:



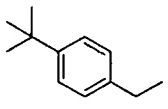
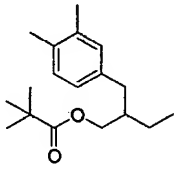
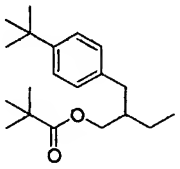
(VI)

wherein

R_1 is a halogen-substituted or unsubstituted lower alkylsulfone having 1 to 5 carbon atoms, arylsulfonyl group or lower alkylcarbonyl group having 1 to 5 carbon atoms;

R_2 is a hydrogen atom, a methoxyl group or a halogen atom;

R_3 is a hydrogen atom, a methoxyl group or a halogen atom;

B is  ,  or  group.

10. The compound according to claim 9 wherein said compound is N-hydroxy-N-[4-(methylsulfonylamino)benzyl]-2-(4-*tert*-butylphenyl)acetamide.

11. A pharmaceutical composition comprising the compound of general formula (I) as set forth in claim 1 as an active ingredient in amount effective amount for an antagonist of vanilloid receptor together with pharmaceutically acceptable carriers or diluents.

12. A pharmaceutical composition comprising the compound of general formula (I) as set forth in claim 1 as an active ingredient in amount effective to alleviate or treat pain diseases or inflammatory diseases together with pharmaceutically acceptable carriers, excipients or diluents.

13. A pharmaceutical composition comprising an efficient amount of the compound represented by general formula (II) as set forth in claim 6 as an active ingredient in amount effective for an antagonist of vanilloid receptor together with pharmaceutically acceptable carriers or diluents.

14. A pharmaceutical composition comprising the compound of general formula (II) as set forth in claim 6 as an active ingredient in amount effective amount to alleviate or treat pain disease together with pharmaceutically acceptable carriers or diluents.

15. The pharmaceutical composition according to claim 12 or 14 wherein said pain disease is at least one selected from the group consisting of pain, acute pain, chronic pain, neuropathic pain, post-operative pain, migraine, arthralgia, neuropathies, nerve injury, diabetic neuropathy, neurodegeneration, neurotic skin disorder, stroke, urinary bladder hypersensitiveness, irritable bowel syndrome, a respiratory disorder such as asthma or chronic obstructive pulmonary disease, irritation of skin, eye or mucous membrane, fervescence, stomach-duodenal ulcer, inflammatory bowel disease caused by the vanilloid receptor antagonistic activity.

16. A pharmaceutical composition comprising the compound of any one of claims 1 to 10 as an active ingredient in amount effective for analgesic and anti-inflammation together with pharmaceutically acceptable carriers or diluents.

17. A pharmaceutical composition comprising the compound of any one of claims 1 to 10 as an active ingredient together with pharmaceutically acceptable carriers or diluents for preventing and treating urgent urinary incontinence.

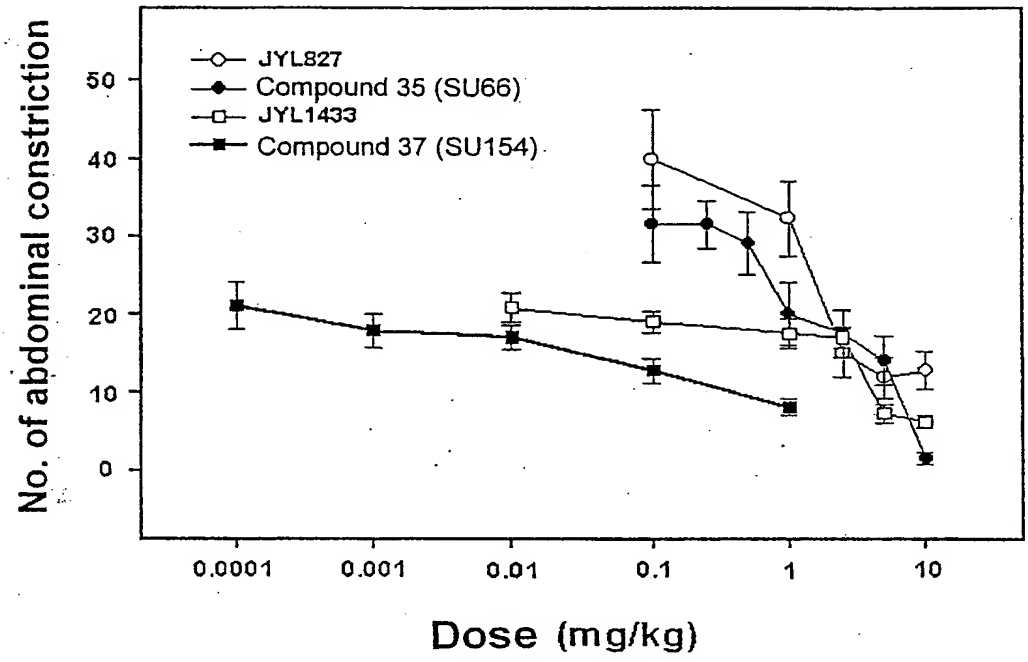
18. Use of the compound of any one of claim 1 to 10 for the preparation of therapeutic agent for the preventing and treating pain disease or inflammatory disease by showing vanilloid receptor-antagonistic activity in human or mammal.

ABSTRACT

The present invention relates to novel n-hydroxythiourea, urea and amide compounds as a potent vanilloid receptor antagonist and the pharmaceutical compositions comprising the same.

The inventive compound can be useful for analgesics to prevent, alleviate or treat pain diseases or inflammatory disease comprising pain, acute pain, chronic pain, neuropathic pain, post-operative pain, migraine, arthralgia, neuropathies, nerve injury, diabetic neuropathy, neurodegeneration, neurotic skin disorder, stroke, urinary bladder hypersensitiveness, irritable bowel syndrome, a respiratory disorder such as asthma or chronic obstructive pulmonary disease, irritation of skin, eye or mucous membrane, fervescence, stomach-duodenal ulcer, inflammatory bowel disease, inflammatory disease and urgent urinary incontinence.

Fig. 1


JYL827
Compound 35 (SU66)
JYL1433
Compound 37 (SU154)
No. of abdominal constriction
0
10
20
30
40
50
0.0001
0.001
0.01
0.1
1
10
Dose (mg/kg)

대한민국특허청
KOREAN INTELLECTUAL PROPERTY OFFICE

별첨 사본은 아래 출원의 원본과 동일함을 증명함.

This is to certify that the following application annexed hereto is a true copy from the records of the Korean Intellectual Property Office.

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Application Number

출 원 년 월 일 : 2002년 10월 17일
Date of Application OCT 17, 2002

출 원 인 : (주) 디지탈바이오텍 외 1명
Applicant(s) DIGITALBIOTECH CO., LTD., et al.

2005 년 02 월 04 일

특 허 청
COMMISSIONER

CERTIFIED COPY OF
PRIORITY DOCUMENT

【서지사항】

【서류명】	특허출원서
【권리구분】	특허
【수신처】	특허청장
【제출일자】	2002.10.17
【발명의 명칭】	신규 엔-하이드록시 티오우레아, 우레아 및 아미드계 화합물 및 이를 함유하는 약제학적 조성물
【발명의 영문명칭】	Novel N-hydroxy thiourea, urea and amide compounds and the pharmaceutical compositions containing the same
【출원인】	
【명칭】	주식회사 디지탈바이오텍
【출원인코드】	1-2000-029482-9
【출원인】	
【성명】	이지우
【출원인코드】	4-1995-114553-0
【대리인】	
【성명】	신동인
【대리인코드】	9-2000-000156-1
【포괄위임등록번호】	2002-038612-4
【포괄위임등록번호】	2002-037533-3
【발명자】	
【성명】	이지우
【출원인코드】	4-1995-114553-0
【심사청구】	청구
【취지】	특허법 제42조의 규정에 의한 출원, 특허법 제60조의 규정에 의한 출원심사 를 청구합니다. 대리인 신동인 (인)
【수수료】	
【기본출원료】	20 면 29,000 원
【가산출원료】	68 면 68,000 원
【우선권주장료】	0 건 0 원
【심사청구료】	15 항 589,000 원

【합계】	686,000 원
【감면사유】	중소기업
【감면후 수수료】	343,000 원
【첨부서류】	1. 요약서·명세서(도면)_1통 2.중소기업기본법시행령 제2조에의한 중소기업에 해당함을 증명하는 서류_1통

【요약서】

【요약】

본 발명은 바닐로이드 수용체-1(Vanilloid Receptor-1; VR1)에 대한 길항제로서 신규한 N-하이드록시 티오우레아, 우레아 및 아미드계 (N-hydroxy thiourea, urea and amide) 유도체 화합물 및 이를 함유하는 약학조성물에 관한 것으로서, 통증(급성통증, 만성통증, 염증성통증, 신경병적 통증, 수술후 통증, 편두통, 관절통), 신경병증(신경손상, 당뇨병성 신경병, 신경변성 질환, 신경성 피부질환), 뇌졸증, 방광과민성, 과민성 장증후군, 천식과 만성폐색성 폐질환 등 호흡기 이상, 피부, 눈, 점막의 자극, 소양증, 발열, 위-십이지장궤양, 염증성 장 질환 및 염증성 질환 등의 예방 및 치료를 위한 약학적 조성물을 제공한다.

【대표도】

도 1

【색인어】

바닐로이드 수용체-1, 길항제, 통증, 신경병증, 약학조성물

【명세서】

【발명의 명칭】

신규 엔-하이드록시 티오우레아, 우레아 및 아미드계 화합물 및 이를 함유하는 약제학적 조성물{Novel N-hydroxy thiourea, urea and amide compounds and the pharmaceutical compositions containing the same}

【도면의 간단한 설명】

도 1 은 선행 특허인 티오우레아계 화합물(JYL-827, JYL-1433)과 본원의 N-하이드록시 티오우레아계 화합물 35(SU-66) 및 화합물 37(SU-154)의 초산유도 라이팅 진통효과를 비교한 도이다.

【발명의 상세한 설명】

【발명의 목적】

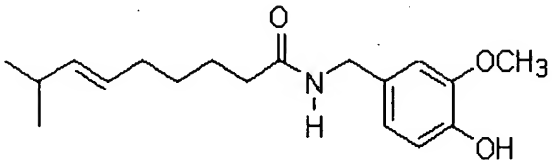
【발명이 속하는 기술분야 및 그 분야의 종래기술】

<2> 본 발명은 바닐로이드 수용체의 강력한 길항제로서 사용하는 N-하이드록시 티오우레아, 우레아 및 아미드계 유도체 및 이를 함유하는 약제학적 조성물에 관한 것이다.

<3> 고추는 향신료로서 뿐만 아니라 전통의약으로서 위장질환, 특히 국소적용으로서 통증, 염증의 치료제로 오랫동안 사용되어 왔으며(Szallasi and Blumberg, *Pharm. Rev.* 51, pp159-211, 1999), 고추의 주된 신미성분인 하기 화학식 1의 캡사이신(capsaicin; 8-methyl-N-vanillyl-6-nonenamide)은 아주 다양한 생리활성을 나타내는데 심혈관계, 호흡계에

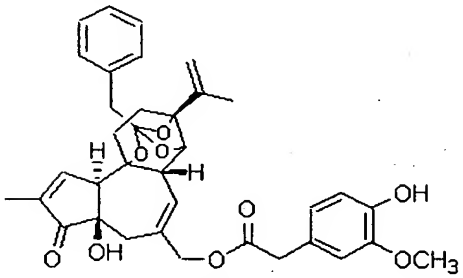
강력한 자극성을 나타낼 뿐만 아니라 국소적용시 통증과 자극성을 유발한다. 그러나 캡사이신은 이러한 통증유발 후에 탈감작(desensitization)을 유도해 캡사이신 자체뿐만 아니라 다른 유해자극에 대해서도 통증을 느끼지 못하게 하는데, 이러한 특성을 활용해 캡사이신, 올바닐, 누바닐, DA-5018, SDZ-249482, 하기 화학식 2의 레시니페라톡신(resiniferatoxin) 등의 유사체가 진통제, 요실금 치료제 또는 피부질환 치료제로 사용되고 있거나 개발중에 있다 (Wriggleworth and Walpole, *Drugs of the Future,* 23, pp531-538, 1998).

<4> 【화학식 1】



캡사이신

<5> 【화학식 2】



레시니페라톡신

<6> 기계적, 열적, 화학적 유해자극에 대한 전도는 주로 가는 무수신경(C-섬유)과 얇은 유수신경(Aδ-섬유)의 일차 구심성 신경섬유가 담당하는데 캡사이신과 바닐로이드(vanilloid)로 통

칭되는 그 유사체의 주된 작용점도 바로 이들 유해감각을 전달하는 신경섬유에 존재한다. 캡사이신은 이들 신경에 존재하는 수용체에 작용해 칼슘, 나트륨 등의 일가 내지 이가 양이온을 강력하게 유입시킴으로서 초기에 강력한 자극을 일으킨 다음 신경기능을 차단함으로서 강력한 진통효과를 발휘한다(Wood et al., *J. Neurosci.*, 8, pp3208-3220, 1988).

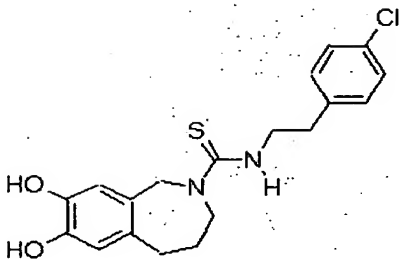
<7> 바닐로이드 수용체는(VR-1) 캡사이신 및 레시니페라톡신과 같은 자극성 화합물을 인식하는 신경막상의 수용체로서 칼슘(Ca^{2+}) 등의 양이온에 선택적인 이온채널로 알려져 있으며, 최근에야 클로닝되어 그 존재가 확실해졌는데(Caterina et al., *Nature*, 389, pp816-824, 1997), 이 수용체는 캡사이신류(바닐로이드) 뿐만 아니라 프로톤, 열자극 등 다양한 유해자극도 전도함이 밝혀졌다(Tominaga et al., *Neuron*, 21, pp531-543, 1998). 이러한 작용으로 보아 바닐로이드 수용체는 다양한 유해자극에 대한 통합적 조절자로서의 역할을 가져 통증 및 유해자극 전달에 핵심적인 기능을 수행할 것으로 판단되며, 최근에는 바닐로이드 수용체의 유전자가 제거된 녹아웃 마우스가 제조되었는데(Caterina et al., *Science*, 288, pp306-313, 2000 : Davis et al., *Nature,* 405, pp183-187, 2000), 일반행동에 있어선 정상 마우스와 차이가 없고 열자극, 열성 통각과민에 대해선 그 반응이 현저히 감약된 것으로 나타나 유해감각 전달에서의 이 수용체의 중요성을 재확인시켜 주었다. 그런데 캡사이신같은 외인성 리간드가 아닌 실제 바닐로이드 수용체에서 유해자극 전달에 관여하는 내인성 리간드는 프로톤 외에는 잘 알려지지 않았는데, 본 연구진의 결과 등에 의하면 12-하이드로프록시아이코사테트라노익산(12-HPETE)으로 대표되는 류코트라이엔(leucotriene)류 대사체(Hwang et al., *PNAS*, 11, pp6155-6160, 2000)와 아난다마이드(anandamide) 등의 아라키도산 유도체(Zygmunt et al., *Trends in Pharmacol. Sci*. 21, pp43-44, 2000)가 이 수용체에 대한 유력한 내인성 리간드로서 작용하고 프로톤은 직접적인 리간드이기 보다는 수용체 활성 항진작용을 지닌 보조인자로 판단된다.

<8> 이와 같이 캡사이신 반응성 감각신경세포 및 그 세포에 존재하는 바닐로이드 수용체는 전신에 분포해 통증, 유해자극 전달에서의 기본적인 기능 외에도, 신경성 염증의 발현에도 역시 중요인자로 작용해서 천식, 과민성 방광질환, 과민성 대장증상, 피부질환의 병인과 밀접한 관련성을 지니고 최근에는 신경변성 질환과의 상관성도 제시되고 있다(WO 99/00125). 최근에는 위장관 손상에서 캡사이신에 반응성을 나타내는 구심성 감각신경의 역할이 특히 주목받고 있는데, 구심성 신경은 CGRP(calcitonin gene-related peptide) 등의 말초 신경펩티드를 유리해 위장 미세혈류를 개선하고 위손상에 대한 방어작용을 나타낼 뿐만 아니라 교감신경계를 자극해 위장손상을 유발하는 이중적 성격을 발휘할 가능성도 제시되었다(Ren et al., *Dig. Dis. Sci.*, 45, pp830-836, 2000). 바닐로이드 수용체 길항제는 이와 같이 다양한 기능을 수행하는 바닐로이드 수용체를 차단함으로서 상기의 다양한 질환군에 대해 예방 또는 치료 목적으로 사용될 수 있는 가능성이 매우 높다고 판단된다.

<9> 바닐로이드 수용체의 길항제 진통기전을 살펴보면, 아난다아마이드 또는 HETE 등의 내인성 통증유발물질이 수용체 결합으로 신경세포에 양이온이 유입되어 통증전달이 진행되며, 길항제는 통증유발물질과 수용체에 결합하는 것을 경쟁적으로 억제하므로, 효현제(agonist)에서 발견되는 초기 자극성의 부작용이 없는 진통제로서 사용될 수 있는 장점을 가지고 있다.

<10> 이러한 바닐로이드 수용체 길항제(antagonist)로는 하기 화학식 3의 캡사제핀(capsazepine), 캡사조케인(capsazocaine)과 루테니움복합제(ruthenium complex)가 현재까지 알려져 있으나, 캡사조케인의 경우 수용체 수준에서의 길항효과가 보고되지 않았고, 염색제로 알려진 루테니움 레드(ruthenium red)인 경우, 비경쟁적(noncompetitive) 길항제로 알려졌다. 그러므로 진정한 수용체 경쟁적(competitive) 길항제는 캡사제핀(capsazepine)뿐으로 진통제 개발 대상으로 많은 관심과 요구가 있어 왔다.

<11> 【화학식 3】



캡사제핀

<12> 본 발명자들은 이러한 이론적 배경에 근거하여 연구를 거듭한 결과, 바닐로이드 수용체의 활성을 억제하는 강력한 길항제로 사용할 수 있는 신규한 N-(4-술포닐아미도)벤질 티오우레아계 및 (4-술포닐아미도)페닐 아세트아미드계 유도체 화합물을 합성하게 되어 본 발명을 완성하였다.

<13> 본 발명자가 개발한 선행 특허의 티오우레아계 화합물(한국특허출원 제 2001-0050092호, 제 2001-0050093호)로부터 이들 화합물이 갖고 있는 높은 지용성을 낮추고, 진통활성을 증가할 목적으로 질소원자 위에 수산기(OH)가 부가된 N-히드록시티오우레아(N-hydroxythiourea), N-히드록시우레아(N-hydroxyturea), N-히드록시아미드(N-hydroxyamide) 유도체를 합성하여 용해도 및 진통활성이 우수한 약물로 개발하여 이를 출원하고자 한다.

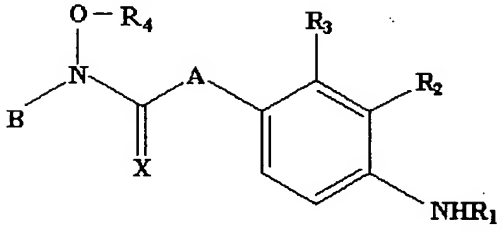
【발명이 이루고자 하는 기술적 과제】

<14> 본 발명의 목적은 강력한 바닐로이드 수용체 길항제로서 유용한 N-하이드록시 티오우레아, 우레아 및 아미드계 유도체 및 이를 함유하는 약학적 조성물을 제공하고자 하는 것이다.

【발명의 구성】

<15> 상기 목적을 달성하기 위하여, 본 발명은 강력한 바닐로이드 수용체 길항제로서 유용한 하기 일반식 (Ⅰ)로 표기되는 화합물, 이들의 약학적으로 허용가능한 염 또는 그 이성질체를 제공한다.

<16> 【화학식 4】

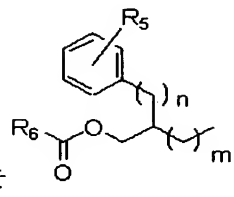


(Ⅰ)

<17> 상기의 식에서,

<18> X는 황원자 또는 산소원자이며;

<19> A는 아미노메틸렌기 또는 메틸렌기이며,

<20> B는 4-*tert*-부틸벤질, 3,4-디메틸페닐프로필, 올레일기 또는 

(Ⅰ-1) (식 중 m은 0 또는 1, n은 1 또는 2)이고,

<21> R_1은 할로겐으로 치환 또는 비치환된 탄소수 1 내지 5의 저급 알킬설폰, 아릴설폰 또는 탄소수 1 내지 5의 저급 알킬카보닐기이며;

<22> R_2은 수소원자, 메톡시기 또는 할로겐기이며;

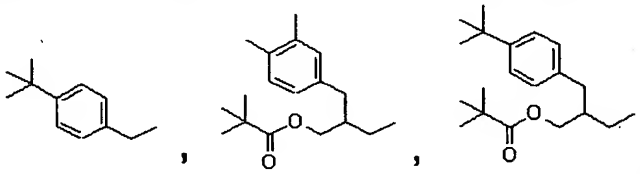
<23> R_3는 수소원자, 메톡시기 또는 할로겐기이며;

<24> R_4는 수소원자 또는 탄소수 1 내지 5의 알킬기이며;

<25> R_5는 수소원자, 탄소수 1 내지 5의 저급 알킬기이며;

<26> R_6는 탄소수 1 내지 5의 저급알킬기 또는 페닐기이다.

<27> 본 발명은 또한, 상기 화학식(Ⅰ)의 화합물 또는 약제학적으로 허용가능한 그의 염을 유효성분으로 포함하는 약제학적 조성물을 제공한다.

<28> 상기 일반식 (Ⅰ)에서, R_1은 메틸술포닐기이고, R_2는 수소원자, 메톡시기 또는 할로겐기이고, R_3는 수소원자, 할로겐기이고, R_4는 수소원자이고, X는 황원자 또는 산소원자이고, A는 아미노메틸렌기이고, B는  인 제 1군의 화합물군으로서, 하기 일반식 (Ⅲ)으로 표기되는 화합물 또는 그 이성질체를 포함하며, 바람직하게는

<29> N-(4-*tert*-부틸벤질)-N-히드록시-N-[4-(메틸술포닐아미노)벤질]티오우레아,

<30> N-(4-*tert*-부틸벤질)-N-히드록시-N-[3-메톡시-4-(메틸술포닐아미노)벤질]티오우레아,

<31> N-(4-*tert*-부틸벤질)-N-히드록시-N-[3-플루오로-4-(메틸술포닐아미노)벤질]티오우레아,

<32> N-(4-*tert*-부틸벤질)-N-히드록시-N-[3-클로로-4-(메틸술포닐아미노)벤질]티오우레아,

<33> N-(4-*tert*-부틸벤질)-N-히드록시-N-[4-(메틸술포닐아미노)-3-니트로벤질]티오우레아,

<34> N-(4-*tert*-부틸벤질)-N-히드록시-N-[2-플루오로-4-(메틸술포닐아미노)벤질]티오우레아,

<35> N-(4-*tert*-부틸벤질)-N-히드록시-N-[2-클로로-4-(메틸술포닐아미노)벤질]티오우레아,

<36> N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[4-(메틸술포닐아미노)벤질]티오우레아,

<37> N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[3-메톡시-4-(메틸술포닐아미노)벤질]티오우레아,

<38> N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[3-플루오로-4-(메틸술포닐아미노)벤질]티오우레아,

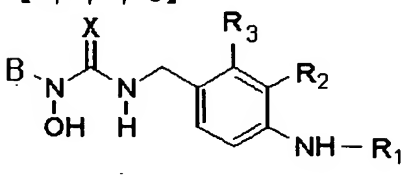
<39> N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[2-플루오로-4-(메틸술포닐아미노)벤질]티오우레아,

<40> N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[2-클로로-4-(메틸술포닐아미노)벤질]티오우레아,

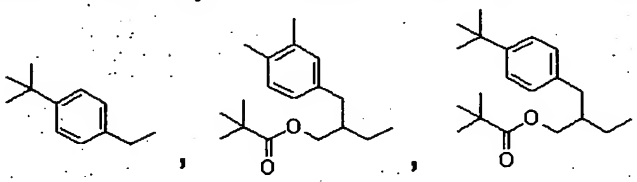
<41> N-[2-(4-*tert*-부틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[4-(메틸술포닐아미노)벤질]티오우레아,

<42> N-[2-(4-*tert*-부틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[3-플루오로-4-(메틸술포닐아미노)벤질]티오우레아를 포함한다.

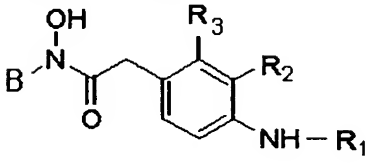
<43> 【화학식 5】



(Ⅲ)

<44> 상기 일반식 (Ⅰ)에서, R_1은 메틸술포닐기이고, R_2는 수소원자, 메톡시기 또는 할로겐기이고, R_3는 수소원자 또는 할로겐기이고, R_4는 수소원자이고, X는 산소원자이고, Y는 질소원자이고, A는 메틸렌기이고, B는  인 제 2군의 화합물군으로서, 하기 일반식 (Ⅳ)로 표기되는 화합물 또는 그 이성질체를 포함하며, 바람직하게는 N-(4-*tert*-부틸벤질)-N-히드록시-[4-(메틸술포닐아미노)페닐]아세트아미드를 포함한다.

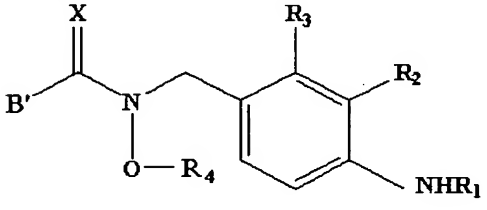
<45> 【화학식 6】



(Ⅳ)

<46> 또한, 본 발명은 강력한 바닐로이드 수용체 길항제로서 유용한 하기 일반식 (Ⅱ)로 표기되는 화합물, 이들의 약제학적으로 허용가능한 염 또는 그 이성질체를 제공한다.

<47> 【화학식 7】

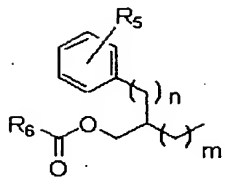


(Ⅱ)

<48> 상기의 식에서,

<49> X는 황원자 또는 산소원자이며;

<50> B'는 상기에서 정의된 B 또는 B로 치환된 2급 아민기이며;

<51> B는 4-*tert*-부틸벤질, 3,4-디메틸페닐프로필, 올레일기 또는  (Ⅱ-1) (식 중 m은 0 또는 1, n은 1 또는 2)이고,

<52> R_1은 할로겐으로 치환 또는 비치환된 탄소수 1 내지 5의 저급알킬설폰, 아릴설폰 또는 탄소수 1 내지 5의 저급알킬카보닐기이며;

<53> R_2은 수소원자, 메톡시기 또는 할로겐기이며;

<54> R_3는 수소원자, 메톡시기 또는 할로겐기이며;

<55> R_4는 수소원자 또는 탄소수 1 내지 5의 알킬기이며;

<56> R_5는 수소원자, 탄소수 1 내지 5의 저급알킬기이며;

<57> R_6는 탄소수 1 내지 5의 저급알킬기 또는 페닐기이다.

<58> 본 발명은 또한, 상기 화학식 (Ⅱ)의 화합물 또는 약학적으로 허용가능한 그의 염을 유효성분으로 포함하는 약학조성물을 제공한다.

<59> 상기 화학식 (Ⅱ)에서, B'는 상기에서 정의된 B로 치환된 2급 아민기이고, R_1은 메틸술포닐기이고, R_2는 수소원자 또는 할로겐기이고, R_3는 수소원자이고, R_4는 수소원자이고, X는 황원자 또는 산소원자인 제 3군의 화합물군으로서, 하기 일반식 (Ⅴ)로 표기되는 화합물 또는 그 이성질체를 포함하며, 바람직하게는

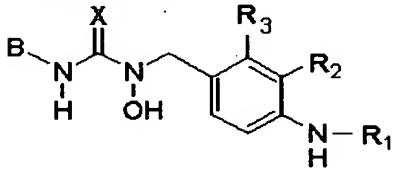
<60> N-(4-*tert*-부틸벤질)-N-하드록시-N-[4-(메틸술포닐아미노)벤질]티오우레아,

<61> N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[4-(메틸술포닐아미노)벤질]티오우레아,

<62> N-(4-*tert*-부틸벤질)-N-히드록시-N-[4-(메틸술포닐아미노)벤질]우레아,

<63> N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[3-플로로-4-(메틸술포닐아미노)벤질]티오우레아를 포함한다.

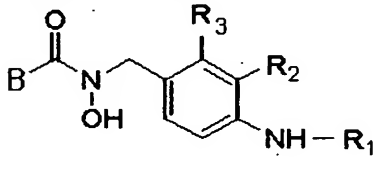
<64> 【화학식 8】



(V)

<65> 상기 일반식 (Ⅱ)에서, B'는 상기에서 정의된 B 치환기이고, R_1은 메틸술포닐기이고, R_2는 수소원자, 메톡시기 또는 할로겐기이고, R_3는 수소원자, 할로겐기이고, R_4는 수소원자이고, X는 산소원자인 제 4군의 화합물군으로서, 하기 일반식 (Ⅵ)으로 표기되는 화합물 또는 그 이성질체를 포함하며, 바람직하게는 N-히드록시-N-[4-(메틸술포닐아미노)벤질]-2-(4-*tert*-부틸페닐)아세트아미드를 포함한다.

<66> 【화학식 9】



(Ⅵ)

<67> 상기 일반식 (Ⅰ) 또는 일반식 (Ⅱ)로 표시되는 본 발명의 화합물들은 당해 기술분야에서 통상적인 방법에 따라 약학적으로 허용가능한 염 및 용매화물로 제조될 수 있다. 염으로는 약학적으로 허용가능한 유리산 (free acid)에 의해 형성된 산부가염이 유용하다. 산 부가염은 통상의 방법, 예를 들면 화합물을 과량의 산 수용액에 용해시키고, 이 염을 수혼화성 유기용매, 예를 들면 메탄올, 에탄올, 아세톤 또는 아세토니트릴을 사용하여 침전시켜서 제조한다. 동몰량의 화합물 및 물 중의 산 또는 알코올 (예, 글리콜 모노메틸에테르)을 가열하고 이어서 상기 혼합물을 증발시켜서 건조시키거나, 또는 석출된 염을 흡인 여과시킬 수 있다.

<68> 이 때, 유리산으로는 유기산과 무기산을 사용할 수 있으며, 무기산으로는 염산, 인산, 황산, 질산, 주석산 등을 사용할 수 있고 유기산으로는 메탄술폰산, *p*-톨루엔술폰산, 아세트산, 트리플루오로아세트산, 시트르산, 말레인산(maleic acid), 숙신산, 옥살산, 벤조산, 타르타르산, 푸마르산, 만데르산, 프로피온산(propionic acid), 구연산(citric acid), 젖산 (lactic acid), 글리콜산(glycollic acid), 글루콘산(gluconic acid), 갈락투론산, 글루탐산, 글루타르산(glutaric acid), 글루쿠론산(glucuronic acid), 아스파르트산, 아스코르브산, 카본산, 바닐릭산, 하이드로 아이오딕산 등을 사용할 수 있다.

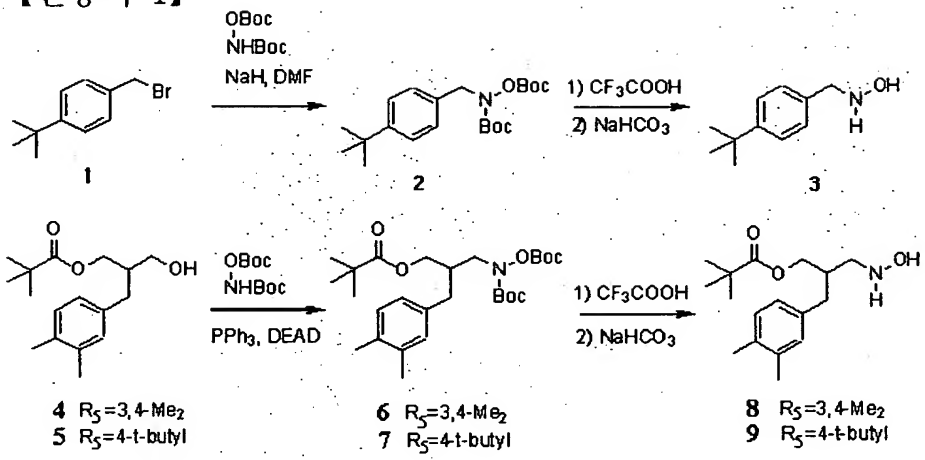
<69> 또한, 염기를 사용하여 약학적으로 허용가능한 금속염을 만들 수 있다. 알칼리 금속 또는 알칼리토 금속염은, 예를 들면 화합물을 과량의 알칼리 금속 수산화물 또는 알칼리토 금속 수산화물 용액 중에 용해하고, 비용해 화합물염을 여과한 후 여액을 증발, 건조시켜 얻는다. 이때, 금속염으로서는 특히 나트륨, 칼륨 또는 칼슘염을 제조하는 것이 제약상 적합하며, 또한 이에 대응하는 은염은 알칼리 금속 또는 알칼리토 금속염을 적당한 은염 (예, 질산은)과 반응시켜 얻는다.

<70> 상기의 일반식 (Ⅰ) 또는 일반식 (Ⅱ)의 약학적으로 허용가능한 염은, 달리 지시되지 않는 한, 일반식 (Ⅰ) 또는 일반식 (Ⅱ)의 화합물에 존재할 수 있는 산성 또는 염기성기의 염을 포함한다. 예를 들면, 약학적으로 허용가능한 염으로는 히드록시기의 나트륨, 칼슘 및 칼륨 염이 포함되며, 아미노기의 기타 약학적으로 허용가능한 염으로는 하이드로브로마이드, 황산염, 수소 황산염, 인산염, 수소 인산염, 이수소 인산염, 아세테이트, 숙시네이트, 시트레이트, 타르트레이트, 락테이트, 만델레이트, 메탄설포네이트(메실레이트) 및 *p*-톨루엔설포네이트(토실레이트) 염이 있으며, 당업계에서 알려진 염의 제조방법이나 제조과정을 통하여 제조될 수 있다.

<71> 또한, 상기의 일반식 (Ⅰ) 또는 일반식 (Ⅱ)의 화합물은 비대칭 중심을 가지므로 상이한 거울상 이성질체 형태로 존재할 수 있으며, 일반식 (Ⅰ) 또는 일반식 (Ⅱ)의 화합물의 모든 광학 이성질체 및 R 또는 S형 입체 이성질체 및 이들의 혼합물도 본 발명의 범주내에 포함되는 것으로 한다. 본 발명은 라세미체, 하나 이상의 거울상 이성질체 형태, 하나 이상의 부분 입체 이성질체 형태 또는 이들의 혼합물의 용도를 포함하며, 당업계에서 알려진 이성질체의 분리 방법이나 제조과정을 포함한다.

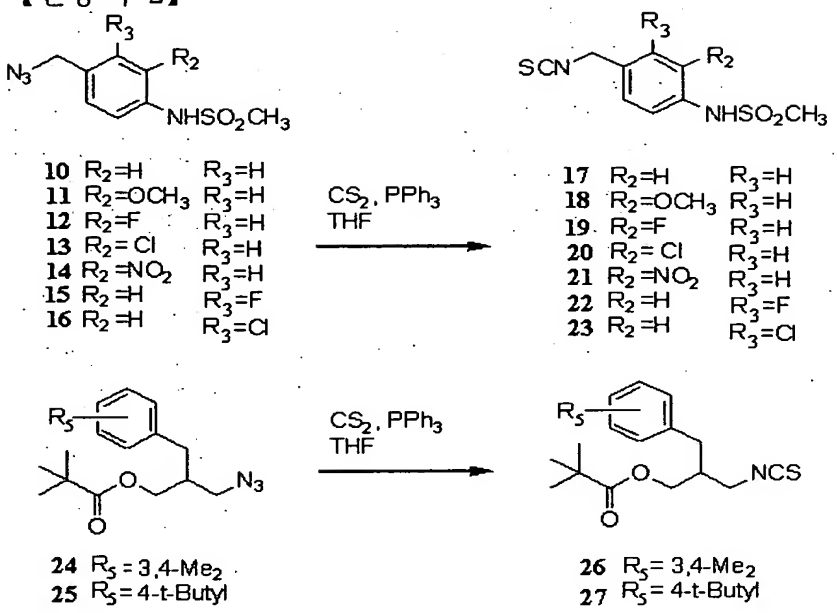
<72> 본 발명의 다른 목적은 상기 일반식 (Ⅰ) 또는 (Ⅱ) 화합물의 제조방법을 제공하는 것으로, 하기의 반응식들에 도시된 방법에 의해 화학적으로 합성될 수 있지만, 이들 예로만 한정되는 것은 아니다. 하기의 반응식들은 본 발명의 대표적인 화합물들의 제조방법을 제조 단계별로 나타내는 것으로 다른 화합물들은 당업자들에 의해 숙지된 시약 및 출발물질의 적당한 변화에 의해 제조될 수 있다.

<73> 【반응식 1】



<74> 상기 반응식 1에서와 같이, 4-*tert*-부틸벤질 브로마이드를 *tert*-부틸-N-(*tert*-부톡시카보닐옥시)카바메이트와 염기조건하에 반응하여 화합물 2를 제조하고, 화합물 2를 산 조건하에 Boc(*tert*-부톡시카보닐)기를 제거하여 히드록실아민 화합물 3을 제조하고, 화합물 4 또는 5를 미쑤노부(Mitsunobu)을 이용하여 *tert*-부틸-N-(*tert*-부톡시카보닐옥시)카바메이트와 축합하여 화합물 6 및 7을 합성할 수 있다. 상기 조건으로 히드록실아민 화합물 8 및 9를 각각 제조할 수 있다.

<75> 【반응식 2】



10 R_2=H R_3=H
11 R_2=OCH_3 R_3=H
12 R_2=F R_3=H
13 R_2= Cl R_3=H
14 R_2=NO_2 R_3=H
15 R_2=H R_3=F
16 R_2=H R_3=Cl

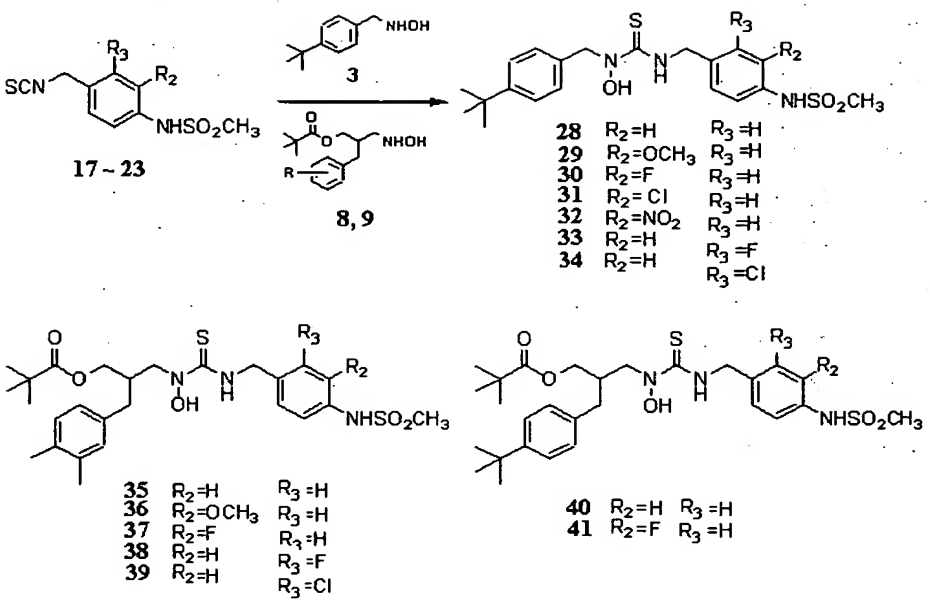
17 R_2=H R_3=H
18 R_2=OCH_3 R_3=H
19 R_2=F R_3=H
20 R_2= Cl R_3=H
21 R_2=NO_2 R_3=H
22 R_2=H R_3=F
23 R_2=H R_3=Cl

24 R_5= 3,4-Me_2
25 R_5= 4-t-Butyl

26 R_5= 3,4-Me_2
27 R_5= 4-t-Butyl

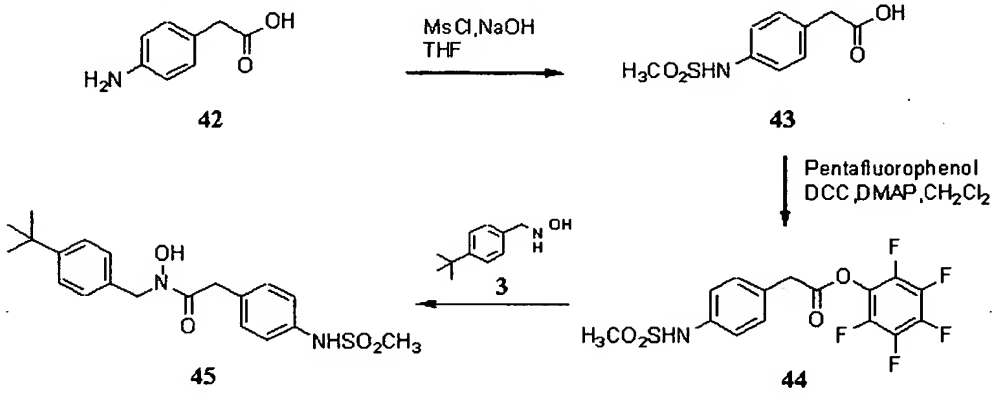
<76> 상기 반응식 2에서와 같이, 한국특허출원 제2001-0050092호 및 제2001-50093호에서 보고된 아지드 화합물 10 내지 16 및 24 내지 25로부터 트리페닐포스핀(triphenylphosphine)과 이황화탄소(carbon disulfide, CS_2)를 이용하여 각각의 이소티오시아네이트(isothiocyanate) 화합물 17 내지 23 및 26 내지 27을 제조할 수 있다.

<77> 【반응식 3】



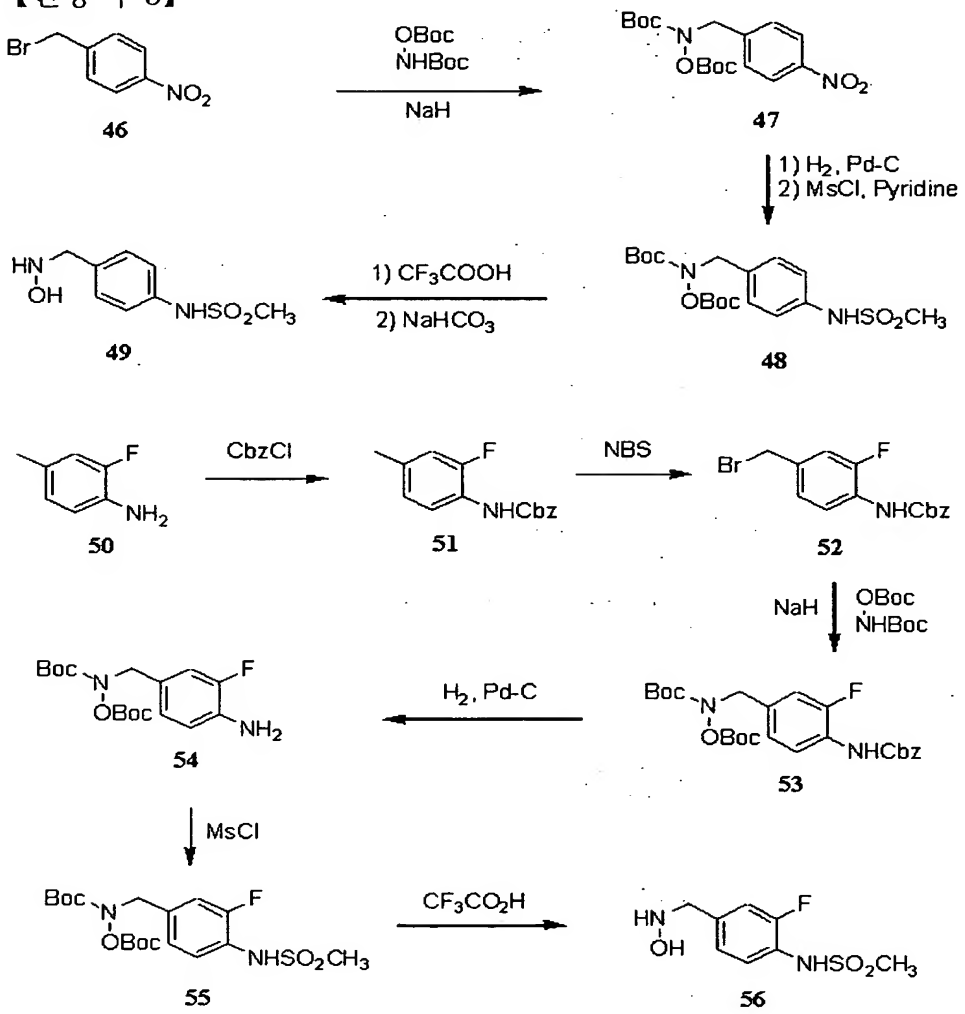
<78> 상기 반응식 3에서와 같이, 반응식 2에서 합성된 이소티오시아네이트 화합물 17 내지 23을 히드록실아민 3, 화합물 8 또는 9와 축합하여, 4-메틸술포닐아미노벤질(methylsulfonylaminobenzyl)기를 갖는 N-히드록시 티오우레아(hydroxy thiourea)계 화합물 28 내지 41을 제조할 수 있다.

<79> 【반응식 4】



<80> 상기 반응식 4에서와 같이, 4-아미노페닐아세트산을 출발물질로 하여 아민기를 메실레이션하고, 산을 펜타플루오르에스테르(pentafluoroester)로 변환한 화합물 44를 제조할 수 있으며, 화합물 44를 히드록실아민 3과 축합하여 4-메틸술포닐아미노벤질(methylsulfonylaminobenzyl)기를 갖는 N-히드록시 아미드계 화합물 45를 제조할 수 있다.

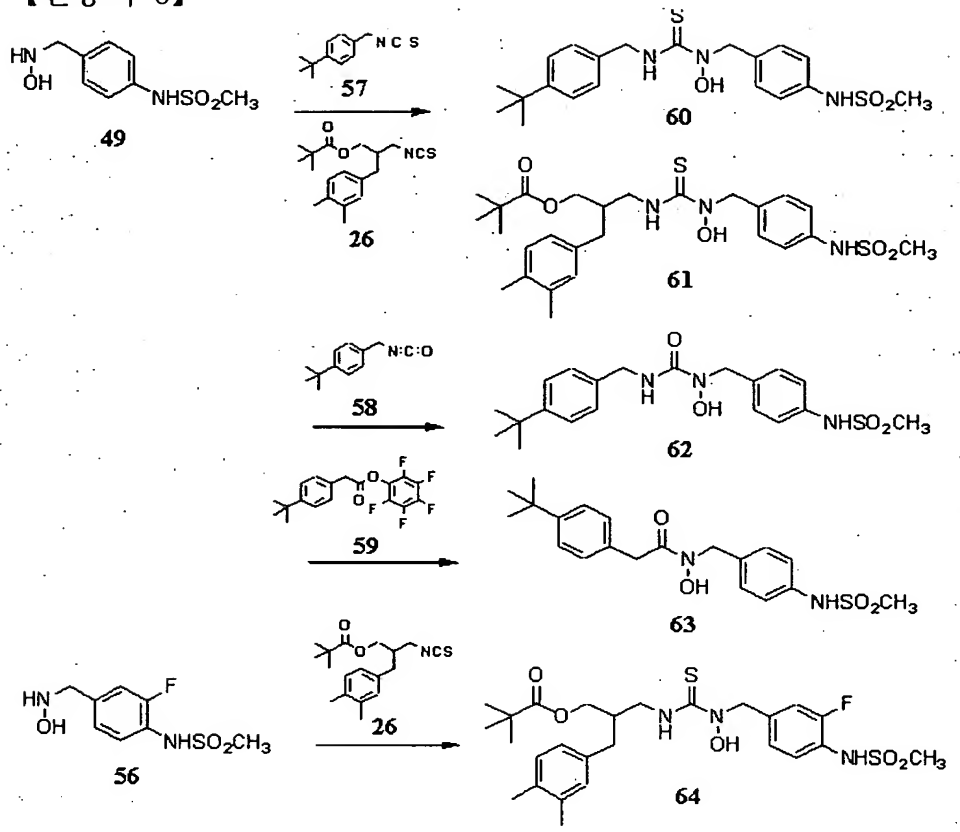
<81> 【반응식 5】



<82> 상기 반응식 5에서와 같이, 4-니트로벤질 브로마이드를 출발물질로 하여 *tert*-부틸-N-(*tert*-부톡시카보닐옥시)카바메이트와 염기조건 하에 반응하여 화합물 47을 제조할 수 있으며, 이로부터 니트로기를 환원한 후 메실레이션하여 화합물 48의 제조가 가능하고, 산 조건하에 Boc 보호기를 제거한 후 중조로부터 히드록실아민 화합물 49를 제조할 수 있다.

<83> 화합물 49의 3-플루오로 유도체 합성은 화합물 50인 2-플루오로-4-메틸아닐린으로부터 출발하여, 화합물 50의 아민기를 카보벤족시기(Cbz, carbobenzoxy)로 보호한 후, 메틸기를 브롬화하여 화합물 52를 제조할 수 있으며, 이 화합물을 *tert*-부틸-N-(*tert*-부톡시카보닐옥시)카바메이트와 염기조건하에 반응하여 화합물 53을 제조할 수 있으며, 화합물 53의 Cbz기를 촉매 환원 조건하에 제거한 후, 메탄설폰기를 축합하여 화합물 55의 제조가 가능하며, 최종적으로 Boc기를 산 조건하에 제거하여 히드록실아민 화합물 56을 제조할 수 있다.

<84> 【반응식 6】



<85> 상기 반응식 6에서와 같이, 히드록실아민 화합물 49를 이소티오시아네이트 57, 화합물 26과 반응하여 N-히드록시티오우레아 화합물 60 및 61을 제조할 수 있고, 이소시아네이트 58과 반응하여 N-히드록시우레아 화합물 70을 제조할 수 있고, 펜타플루오로에스테르 59와 반응하여 화합물 63을 합성하며, 또한 3-F가 붙은 히드록실아민 화합물 56도 이소티오시아네이트 26과 축합하여 N-글렘히드록시티오우레아(glemhydroxythiourea) 화합물 64를 제조할 수 있다.

<86> 본 발명의 또 다른 목적은 활성성분으로써 통증을 완화시키는데 유효 활성 성분으로 한 상기 일반식 (Ⅰ) 또는 일반식 (Ⅱ) 화합물과 약제학적으로 허용 가능한 담체, 보조제 또는 희석액과 함께 함유하는 바닐로이드 수용체의 길항 활성을 갖는 약학 조성물을 제공하는 것이다.

<87> 상기의 통증은 통증, 통증, 급성 통증, 만성 통증, 신경병적 통증, 수술후 통증, 편두통, 관절통, 신경병증, 신경손상, 당뇨병성 신경병, 신경변성 질환, 신경성 피부질환, 뇌졸중, 방광과민증, 과민성 장증후군, 천식과 만성폐색성 폐질환 등 호흡기 이상, 피부, 눈, 점막의 자극, 발열, 위-십이지장궤양, 염증성 장 질환 또는 이들 염증성 질환 및 급박성 요실금 질환을 포함한다.

<88> 또한, 본 발명은 상기 일반식 (Ⅰ) 또는 일반식 (Ⅱ) 화합물을 유효성분으로 하고, 약학적으로 허용되는 담체를 포함하는 소염 및 진통의 예방 및 치료용 조성물을 제공한다.

<89> 마찬가지로, 본 발명은 상기 일반식 (Ⅰ) 또는 일반식 (Ⅱ) 화합물을 유효성분으로 하고, 약학적으로 허용되는 담체를 포함하는 급박성 요실금 질환의 예방 및 치료용 조성물을 제공한다.

<90> 본 발명의 소염, 진통 또는 요실금용 조성물은, 조성물 총 중량에 대하여 상기 일반식 (Ⅰ) 또는 일반식 (Ⅱ) 화합물을 0.5 ~ 50 중량 %로 포함한다.

<91> 본 발명의 일반식(Ⅰ) 또는 일반식 (Ⅱ) 화합물과 함께 사용할 수 있는 약학적으로 허용가능한 담체, 보조제 또는 희석액으로 예를 들면, 본 발명의 화합물은 주사 용액의 제조에 통상적으로 사용되는 오일, 프로필렌글리콜 또는 다른 용매에 용해시킬 수 있다. 적당한 담체로는 특별히 한정되지 않지만, 예를 들면, 생리식염수, 폴리에틸렌글리콜, 에탄올, 식물성 오일 및 이소프로필미리스테이트 등이 있다. 국소 적용을 위해서는 본 발명의 화합물을 연고나 크림으로 제형화할 수 있다.

<92> 이하, 제형방법 및 부형제를 설명하지만, 이들 예로만 한정되는 것은 아니다.

<93> 본 발명의 화합물의 약학적 투여 형태는 이들의 약학적 허용가능한 염의 형태로도 사용될 수 있고, 또한 단독으로 또는 타 약학적 활성 화합물과 결합뿐만 아니라 적당한 집합으로 사용될 수 있다.

<94> 본 발명의 화합물은 일반적인 식염수, 5% 덱스트로스와 같은 수용성 용매 또는 식물성 오일, 합성 지방산 글리세라이드, 고급 지방산 에스테르 또는 프로필렌글리콜과 같은 비수용성 용매에 화합물을 용해시키거나, 현탁시키거나 또는 유화시켜 주사제로 제형화될 수 있다. 본 발명의 제형은 용해제, 등장화제(isotonic agents), 현탁화제, 유화제, 안정화제 및 방부제와 같은 종래의 첨가제를 포함할 수 있다.

<95> 본 발명의 화합물의 바람직한 투여량은 환자의 상태 및 체중, 질병의 정도, 약물형태, 투여경로 및 기간에 따라 다르지만, 당업자에 의해 적절하게 선택될 수 있다. 그러나, 바람직한 효과를 위해서, 본 발명의 화합물은 1일 0.0001~100mg/kg으로, 바람직하게는 0.001~100mg/kg으로 투여하는 것이 좋다. 투여는 하루에 한번 투여할 수도 있고, 수회 나누어 투여할 수 있다. 조성물에서 본 발명의 화합물은 전체 조성물 총 중량에 대하여 0.0001 ~ 10 중량%, 바람직하게는 0.001 ~ 1 중량%의 양으로 존재하여야 한다.

<96> 본 발명의 약학 조성물은 쥐, 마우스, 가축, 인간 등의 포유동물에 다양한 경로로 투여될 수 있다. 투여의 모든 방식은 예상될 수 있는데, 예를 들면, 경구, 직장 또는 정맥, 근육, 피하, 자궁내 경막 또는 뇌혈관내 (intracerebroventricular) 주사에 의해 투여될 수 있다.

<97> 이하 본 발명을 실시예 및 실험예에 의해 상세히 설명한다.

<98> 단, 하기 실시예 및 실험예는 본 발명을 예시하는 것일 뿐, 본 발명의 내용이 한정되는 것은 아니다.

<99> 실시예 1. *tert*-부틸 N-[(*tert*-부톡시카보닐)옥시]-N-(4-*tert*-부틸벤질)카바메이트 화합물(2) 제조

<100> 0℃ DMF 20㎖에 용해된 화합물인 *tert*-부틸-N-(*tert*-부톡시카보닐옥시)카바메이트 5g(21.4 mmol)에 수소화나트륨(NaH, Sodium hydride) 12.8g(60%, 32.1mmol)을 넣어서 실온에서 30분동안 용해시키고, 반응혼합물은 4-*t*-부틸벤질브로마이드 7.3g(32.1mmol)과 같이 처리하여 실온에서 18시간동안 교반한다. 물로 희석하고, 수회 에틸아세테이트로 추출한 후, 유기층을 황산 마그네슘으로 건조시키고 감압농축하며, 잔사물은 컬럼크로마토그래피(전개용매: 헥산/에틸아세테이트=1:10)로 분리하여 무색의 오일인 *tert*-부틸 N-[(*tert*-부톡시카보닐)옥시]-N-(4-*tert*-부틸벤질)카바메이트 화합물 7.72g(수율 95%)을 얻었다.

<101> ^{1}H-NMR ($CDCl_3$) δ : 7.35 (dt, 2 H, J = 2.2, 8.5 Hz, Ar), 7.26 (d, 2 H, J = 8.5 Hz, Ar), 4.72 (s, 2 H, CH_2), 1.49 (s, 9 H, $C(CH_3)_3$), 1.44 (s, 9 H, $C(CH_3)_3$), 1.30 (s, 9 H, $C(CH_3)_3$).

<102> 실시예 2. N-[4-*tert*-부틸벤질]히드록실아민 화합물(3) 제조

<103> 염화메틸렌 100㎖에 용해된 상기 실시예 1의 *tert*-부틸 N-[(*tert*-부톡시카보닐)옥시]-N-(4-*tert*-부틸벤질)카바메이트 화합물 7.6(20mmol)을 0℃에서 삼불화아세트산(trifluoroacetic acid) 20㎖에 천천히 적가하여 실온에서 50분간 저어준다. 20℃ 이하에서 감압농축하여 용매를 제거하고, 잔사물은 포화된 탄산수소나트륨과 디에틸 에스

테르 용액으로 분획하였고, 수회에 걸쳐 디에틸 에스테르 용액으로 수층을 추출하였다. 유기층을 물, 생리식염수로 세척하고, 황산마그네슘으로 건조한 후, 감압농축하였으며, 연노랑색의 오일인 N-[4-*tert*-부틸벤질]히드록실아민 화합물 3.58g(수율 100%)을 수득하였다.

<104> ^{1}H-NMR ($CDCl_3$) δ : 7.39 (d, 2 H, J = 8.0 Hz, Ar), 7.27 (d, 2 H, J = 8.0 Hz, Ar), 4.22 (s, 2 H, CH_2), 1.27 (s, 9 H, $C(CH_3)_3$).

<105> 실시예 3. *tert*-부틸 N-[(*tert*-부톡시카보닐)옥시]-N-[2-(3,4-디메틸벤질)-3-피발로일옥시-프로필] 카바메이트 화합물(6) 제조

<106> THF 30㎖에 용해된 *tert*-부틸 N-(*tert*-부톡시카보닐옥시) 카바메이트 (0.92 g, 3.95 mmol) 용액에 디에틸 아조디카복실레이트 0.85㎖(5.39mmol)을 천천히 적가한 후, 실온에서 5분 동안 저어주었으며, 혼합물에 트리페닐포스핀 1.41g(5.39mmol)과 상기의 화합물 4의 1g(3.59mmol)을 한 방울씩 적가하여 실온에서 30분간 저어준 후, 혼합물을 메탄올 5㎖로 반응을 종료하고 감압농축하였다. 잔사물은 컬럼 크로마토그래피(전개용매: 에틸아세테이트/헥산=1:10)로 분리하였으며, 무색의 오일인 *tert*-부틸 N-[(*tert*-부톡시카보닐)옥시]-N-[2-(3,4-디메틸벤질)-3-피발로일옥시-프로필] 카바메이트 화합물 1.6g(수율 90%)을 수득하였다.

<107> ^{1}H-NMR ($CDCl_3$) δ : 6.85-7.05 (m, 3 H, Ar), 3.9-4.1 (m, 2 H, CH_2OCO), 3.67 (bs, 2 H, CH_2N), 2.5-2.9 (m, 2 H, CH_2Ar), 2.18-2.28 (m, 7 H, 2 x CH_3 & CH), 1.53 (s, 9 H, $C(CH_3)_3$), 1.47 (s, 9 H, $C(CH_3)_3$), 1.22 (s, 9 H, $C(CH_3)_3$).

<108> 실시예 4. *tert*-부틸 N-[(*tert*- 부톡시카보닐)옥시]-N-[2-(4-*tert*-부틸벤질)-3-피발로일옥시-프로필] 카바메이트 화합물(7) 제조

<109> 상기의 실시예 3과 동일한 방법으로 수행하였으며, 화합물 5를 이용하여 제조되었고, *tert*-부틸 N-[(*tert*-부톡시카보닐)옥시]-N-[2-(4-*tert*-부틸벤질)-3-피발로일옥시-프로필] 카바메이트 화합물 1.45g(수율 88%)을 수득하였다.

<110> ^{1}H-NMR ($CDCl_3$) δ : 7.29 (d, 2 H, J = 8.3 Hz, Ar), 7.09 (d, 2 H, J = 8.3 Hz, Ar), 4.00 (ddd of AB, 2 H, CH_2OCO), 3.66 (bs, 2 H, CH_2N), 2.79 (dd, 1 H, CH_2Ar), 2.60 (dd, 1 H, CH_2Ar), 2.30 (m, 1 H, CH), 1.52 (s, 9 H, $C(CH_3)_3$), 1.47 (s, 9 H, $C(CH_3)_3$), 1.30 (s, 9 H, $C(CH_3)_3$), 1.22 (s, 9 H, $C(CH_3)_3$).

<111> 실시예 5. N-[2-(3,4-디메틸벤질)-3-피발로일옥시-프로필]히드록실아민 화합물(8) 제조

<112> 상기 실시예 2와 동일한 방법으로 수행하였으며, 반응물은 *tert*-부틸 N-[(*tert*-부톡시카보닐)옥시]-N-[2-(3,4-디메틸벤질)-3-피발로일옥시-프로필] 카바메이트 화합물(6)을 사용하여 N-[2-(3,4-디메틸벤질)-3-피발로일옥시-프로필]히드록실아민 화합물(8) 1.6g(수율 90%)을 수득하였다.

<113> ^{1}H-NMR($CDCl_3$) δ : 6.86-7.06 (m, 3 H, Ar), 5.45 (bs, 1 H), 3.95-4.15 (m, 2 H, CH_2OCO), 2.85-3.02 (m, 2 H, CH_2N), 2.72 (d, 1 H, CH_2Ar), 2.62 (m, 1 H, CH_2Ar), 2.2-2.4 (m, 7 H, 2 x CH_3 & CH)

<114> 실시예 6. N-[2-(4-*tert*- 부틸벤질)-3-피발로일옥시-프로필]히드록실아민 화합물

<115> (9) 제조

<116> 상기 실시예 2와 동일한 방법으로 수행하였으며, 반응물은 *tert*-부틸 N-[(*tert*-부톡시카보닐)옥시]-N-[2-(4-*tert*-부틸벤질)-3-피발로일옥시-프로필] 카바메이트 화합물(7)을 사용하여 N-[2-(3,4-디메틸벤질)-3-피발로일옥시-프로필]히드록실아민 화합물(9) 1.45g(수율 88%)을 수득하였다.

<117> ^{1}H-NMR (CDCl3) δ : 7.30 (d, 2 H, *J* = 8.2 Hz), 7.10 (d, 2 H, *J* = 8.2 Hz), 5.16 (bs, 1 H), 4.06 (ddd of AB, 2 H, *J* = 5, 11.2 Hz, CH_2OCO), 2.95 (ddd of AB, 2 H, *J* = 6, 13 Hz, CH_2 N), 2.67 (ddd of AB, 2 H, *J* = 7, 13.5 Hz, CH_2Ar), 2.33 (m, 1 H, CH), 2.2-2.4 (m, 7 H, 2 x CH_3), 1.30 (s, 9 H, $C(CH_3)_3$), 1.22 (s, 9 H, $C(CH_3)_3$)

<118> 실시예 7. 이소티오시아네이트(isothiocyanate)체의 일반적 합성방법

<119> THF(10㎖)에 아지드(1.0 mmol), 트리페닐포스핀 290mg(1.1 mmol)을 용해한 용액에 수소화나트륨(NaH, Sodium hydride) 0.6㎖(10 mmol)을 처리하고, 1 내지 3시간동안 환류추출하고, 혼합물은 감압농축하였다. 잔사물은 컬럼 크로마토그래피(전개용매: 에틸아세테이트/헥산=1:2)로 분리 및 정제하여 이소티오시아네이트를 수득하였다.

<120> 실시예 8. 4-(메틸술포닐아미노)벤질 이소티오시아네이트 화합물(17) 제조

<121> 상기의 실시예 7과 동일한 방법으로 수행하였으며, 흰색의 고체인 4-(메틸술포닐아미노)벤질 이소티오시아네이트 화합물(17) (수율 63%)을 수득하였다.

<122> 녹는점: 122-124 ℃

<123> ^{1}H-NMR($CDCl_3$) δ: 7.32 (d, 2 H, J = 8.4 Hz) 7.24 (d, 2 H, J = 8.4 Hz), 6.62 (s, 1 H, $NHSO_2$), 4.70 (s, 2 H, CH2) 3.04 (s, 3 H, SO_2CH_3)

<124> 실시예 9. 3-메톡시-4-(메틸술포닐아미노)벤질 이소티오시아네이트 화합물(18) 제조

<125> 상기의 실시예 7과 동일한 방법으로 수행하였으며, 흰색의 고체인 3-메톡시-4-(메틸술포닐아미노)벤질 이소티오시아네이트 화합물(18) (수율 59%)을 수득하였다.

<126> 녹는점: 100-103 ℃

<127> ^{1}H-NMR($CDCl_3$) δ: 7.53 (d, 1 H, J = 8.2 Hz), 6.88-6.92 (m, 2 H), 6.80 (bs, 1 H, $NHSO_2$), 4.68 (s, 2 H, CH_2), 3.92 (s, 3 H, OCH_3), 2.97 (s, 3 H, SO_2CH_3)

<128> 실시예 10. 3-플루오로-4-(메틸술포닐아미노)벤질 이소티오시아네이트 화합물(19) 제조

<129> 상기의 실시예 7과 동일한 방법으로 수행하였으며, 흰색의 고체인 3-플루오로-4-(메틸술포닐아미노)벤질 이소티오시아네이트 화합물(19) (수율 54%)을 수득하였다.

<130> 녹는점: 95-97 ℃

<131> ^{1}H-NMR($CDCl_3$) δ: 7.61 (t, 1 H, J = 8.0 Hz), 7.14 (m, 2 H), 6.53 (bs, 1 H, $NHSO_2$), 4.70 (s, 2 H, CH_2), 3.01 (s, 3 H, SO_2CH_3)

<132> 실시예 11. 3-클로로-4-(메틸술포닐아미노)벤질 이소티오시아네이트 화합물(20) 제조

<133> 상기의 실시예 7과 동일한 방법으로 수행하였으며, 흰색의 고체인 3-클로로-4-(메틸술포닐아미노)벤질 이소티오시아네이트 화합물(20) (수율 48%)을 수득하였다.

<134> 녹는점; 112-113 ℃

<135> ^{1}H-NMR($CDCl_3$) δ: 7.68 (d, 1 H, J = 8.3 Hz), 7.42 (d, 1 H, J = 2.4 Hz), 7.26 (dd, 1 H, J = 8.3, 2.4 Hz), 6.80 (bs, 1 H, $NHSO_2$), 4.70 (s, 2 H, CH_2), 3.04 (s, 3 H, SO_2CH_3)

<136> 실시예 12. 4-(메틸술포닐아미노)-3-니트로벤질 이소티오시아네이트 화합물(21) 제조

<137> 상기의 실시예 7과 동일한 방법으로 수행하였으며, 흰색의 고체인 4-(메틸술포닐아미노)-3-니트로벤질 이소티오시아네이트 화합물(21) (수율 42%)을 수득하였다.

<138> 녹는점; 128-130 ℃

<139> ^{1}H-NMR($CDCl_3$) δ: 8.24 (d, 1 H, J = 2.4 Hz), 7.95 (d, 1 H, J = 8.3 Hz), 7.66 (dd, 1 H, J = 8.3, 2.4 Hz), 4.78 (s, 2 H, CH_2), 3.18 (s, 3 H, SO_2CH_3)

<140> 실시예 13. 2-플루오로-4-(메틸술포닐아미노)벤질 이소티오시아네이트 화합물(22) 제조

<141> 상기의 실시예 7과 동일한 방법으로 수행하였으며, 엷은 노랑색의 오일인 2-플루오로-4-(메틸술포닐아미노)벤질 이소티오시아네이트 화합물(22) (수율 56%)을 수득하였다.

<142> ^{1}H-NMR($CDCl_3$) δ: 7.38 (t, 1 H, J = 8.0 Hz), 7.09 (dd, 1 H, J = 10.9, 2.2 Hz), 6.99 (dd, 1 H, J = 8.3, 2.2 Hz), 4.73 (s, 2 H, CH_2), 3.08 (s, 3 H, SO_2CH_3)

<143> 실시예 14. 2-클로로-4-(메틸술포닐아미노)벤질 이소티오시아네이트 화합물(23) 제조

<144> 상기의 실시예 7과 동일한 방법으로 수행하였으며, 엷은 노랑색의 고체인 2-클로로-4-(메틸술포닐아미노)벤질 이소티오시아네이트 화합물(23) (수율 54%)을 수득하였다.

<145> 녹는점: 110-112 ℃

<146> ^{1}H-NMR ($CDCl_3$) δ: 7.43 (d, 1 H, J = 8.3 Hz), 7.33 (d, 1 H, J = 2.2 Hz), 7.16 (dd, 1 H, , J = 8.3 and 2.2 Hz), 6.79 (bs, 1 H, $NHSO_2$), 4.79 (s, 2 H, CH_2), 3.08 (s, 3 H, SO_2CH_3)

<147> 실시예 15. 2-(3,4-디메틸벤질)-3-피발로일옥시-프로필 이소티오시아네이트 화합물 (26) 제조

<148> 상기의 실시예 7과 동일한 방법으로 수행하였으며, 무색의 오일인 2-(3,4-디메틸벤질)-3-피발로일옥시-프로필 이소티오시아네이트 화합물 (26) (수율 92%)을 수득하였다.

<149> ^{1}H-NMR($CDCl_3$) δ: 6.85-7.1 (m, 3 H, Ar), 3.95-4.2 (m, 2 H, CH2OCO), 3.53 (m, 2 H, CH_2 NCS), 2.55-2.85 (m, 2 H, CH_2Ar), 2.2-2.3 (m, 7 H, 2 x CH_3 and CH), 1.23 (s, 9 H, $C(CH_3)_3$)

<150> 실시예 16. 2-(4-*t*- 부틸벤질)-3-피발로일옥시-프로필 이소티오시아네이트 화합물

<151> (27) 제조

<152> 상기의 실시예 7과 동일한 방법으로 수행하였으며, 무색의 오일인 2-(4-*t*-부틸벤질)-3-피발로일옥시-프로필 이소티오시아네이트 화합물(27) (수율 90%)을 수득하였다.

<153> ^{1}H-NMR($CDCl_3$) δ: 7.33 (d, 2 H, J = 8.3 Hz), 7.10 (d, 2 H, J = 8.3 Hz), 4.15 (dd, 1 H, J = 4.9 , 11.4 Hz, CH_2OCO), 4.01 (dd, 1 H, J = 7 , 11.4 Hz, CH_2OCO), 3.53 (sevenlet, 2 H, CH_2NCS), 2.70 (ddd of AB, 2 H, CH_2Ar), 2.31 (bs, 1 H, CH), 1.31 (s, 9 H, $C(CH_3)_3$), 1.23 (s, 9 H, $C(CH_3)_3$).

<154> 실시예 17. N-히드록시 티오우레아체 화합물의 일반적 합성법

<155> 염화메틸렌 10㎖에 하이드록실아민(1.0 mmol)과 이소티오시아네이트(1.0mmol) 혼합물을 넣고 1 내지 4시간동안 실온에서 저어준 후, 감압농축하였다. 잔사물은 컬럼 크로마토그래피(전개용매: 에틸아세테이트/헥산=1:1)로 분리 및 정제하여 N-하이드록시 티오우레아를 수득하였다.

<156> 실시예 18. N-(4-*tert*-부틸벤질)-N-히드록시-N-[4-(메틸술포닐아미노)벤질]티오우레아 화합물(28) 제조

<157> 상기의 화합물 17과 화합물 3의 혼합물을 사용하여 실시예 17과 동일한 방법으로 수행하였으며, 흰색의 고체인 N-(4-*tert*-부틸벤질)-N-하이드록시-N-[4-(메틸술포닐아미노)벤질] 티오우레아 화합물(28) (수율 94%)을 수득하였다(표 1 참조).

<158> 녹는점: 137 ℃

<159> ^{1}H-NMR($CDCl_3$) δ: 7.38 (s, 4 H), 7.32 (d, 2 H, J = 8.3 Hz), 7.15 (d, 2 H, J = 8.3 Hz), 6.46 (s, 1 H, $NHSO_2$), 5.97 (bs, 1 H, NHCS), 5.34 (s, 2 H, CH_2NOH), 4.82 (d, 2 H, J = 5.6 Hz, $NHCH_2$), 2.97 (s, 3 H, SO_2CH_3), 1.31 (s, 9 H, $C(CH_3)_3$).

<160> IR (KBr): 3350, 2962, 1512, 1336, 1123 cm^{-1}

<161> MS *m/z* : 422 (MH^+)

<162> 실시예 19. N-(4-*tert*-부틸벤질)-N-히드록시-N-[3-메톡시-4-(메틸술포닐아미노)벤질]티오우레아 화합물(29) 제조

<163> 상기의 화합물 18과 화합물 3의 혼합물을 사용하여 실시예 17과 동일한 방법으로 수행하였으며, 흰색의 고체인 N-(4-*tert*-부틸벤질)-N-히드록시-N-[3-메톡시-4-(메틸술포닐아미노)벤질]티오우레아 화합물(29) (수율 92%)를 수득하였다(표 1 참조).

<164> 녹는점: 112.5 - 115 ℃

<165> ^{1}H-NMR ($CDCl_3$) δ : 7.39 (m, 4 H), 6.99 (m, 1 H), 6.91 (m, 1 H), 6.74 (m, 1 H), 5.52 (bs, 1 H, NH), 5.36 (s, 2 H, CH_2NHOH), 4.83 (d, 2 H, J = 5.6 Hz, CH_2NH), 3.88 (s, 3 H, OCH_3), 2.94 (s, 3 H, SO_2CH_3), 1.32 (s, 9 H, $C(CH_3)_3$)

<166> IR (KBr) 3352, 2962, 1513, 1336, 1123 cm^{-1}

<167> MS *m/z*: 452 (MH^+)

<168> 실시예 20. N-(4-*tert*-부틸벤질)-N-히드록시-N-[3-플루오로-4-(메틸술포닐아미노)벤질]티오우레아 화합물(30) 제조

<169> 상기의 화합물 19와 화합물 3의 혼합물을 사용하여 실시예 17과 동일한 방법으로 수행하였으며, 흰색의 고체인 N-(4-*tert*-부틸벤질)-N-히드록시-N-[3-플루오로

<170> -4-(메틸술포닐아미노)벤질]티오우레아 화합물(30) (수율 93%)을 수득하였다(표 1 참조).

<171> 녹는점: 124-126 ℃

<172> ^{1}H-NMR($CDCl_3$) δ : 7.50 (t, 1 H, *J* = 8.0 Hz), 7.38 (AB q, 4 H, *J* = 8.8 Hz), 7.1-7.2 (m, 2 H), 5.34 (s, 2 H, CH_2NOH), 4.85 (d, 2 H, *J* = 5.6 Hz, CH_2NH), 3.00 (s, 3 H, SO_2CH_3), 1.32 (s, 9 H, $C(CH_3)_3$).

<173> IR (KBr): 3260, 2963, 1513, 1326, 1153, 1107 cm^{-1}

<174> MS *m/z* : 440 (MH^+)

<175> 실시예 21. N-(4-*tert*-부틸벤질)-N-히드록시-N-[3-클로로-4-(메틸술포닐아미노)벤질]티오우레아 화합물(31) 제조

<176> 상기의 화합물 20과 화합물 3의 혼합물을 사용하여 실시예 17과 동일한 방법으로 수행하였으며, 흰색의 고체인 N-(4-*tert*-부틸벤질)-N-히드록시-N-[3-클로로-4-(메틸술포닐아미노)벤질]티오우레아 화합물(31) (수율 91%)을 수득하였다(표 1 참조).

<177> 녹는점; 119.5 - 122.5 ℃

<178> ^{1}H-NMR($CDCl_3$) δ : 7.62 (d, 1 H, *J* = 8.5 Hz), 7.44 (d, 1 H, *J* = 2.0 Hz), 7.36-7.42 (m, 3 H), 7.26 (m, 2 H), 5.36 (s, 2 H, $HONCH_2$), 4.86 (d, 2 H, *J* = 5.8 Hz, $NHCH_2$), 3.01 (s, 3 H, SO_2CH_3), 1.32 (s, 9 H, $C(CH_3)_3$).

<179> IR (KBr): 3400, 2919, 1737, 1383, 1216, 1107 cm^{-1}

<180> MS *m/z* 456 (MH^+)

<181> 실시예 22. N-(4-*tert*-부틸벤질)-N-히드록시-N-[4-(메틸술포닐아미노)-3-니트로벤질]티오우레아 화합물(32) 제조

<182> 상기의 화합물 21과 화합물 3의 혼합물을 사용하여 실시예 17과 동일한 방법으로 수행하였으며, 흰색의 고체인 N-(4-*tert*-부틸벤질)-N-히드록시-N-[4-(메틸술포닐아미노)-3-니트로벤질)]티오우레아 화합물(32) (수율 90%)을 수득하였다(표 1 참조).

<183> 녹는점: 102-105 ℃

<184> ^{1}H-NMR ($CDCl_3$) δ: 8.22 (d, 1 H, J = 2.0 Hz, ArH-2), 7.86 (d, 1 H, J = 8.3 Hz, ArH-5), 7.70 (dd, 1 H, J = 2.0, 8.3 Hz, ArH-6), 7.40 (dd, 4 H, Ar), 5.36 (s, 2 H, $HONCH_2$), 4.92 (d, 2 H, J = 5.6 Hz, $NHCH_2$), 3.14 (s, 3 H, SO_2CH_3), 1.32 (s, 9 H, $C(CH_3)_3$)

<185> IR (KBr) 3360, 2919, 1538, 1337, 1143 cm^{-1}

<186> MS *m/z*: 467 (MH^+)

<187> 실시예 23. N-(4-*tert*-부틸벤질)-N-히드록시-N-[2-플루오로-4-(메틸술포닐아미노)벤질]티오우레아 화합물(33) 제조

<188> 상기의 화합물 22와 화합물 3의 혼합물을 사용하여 실시예 17과 동일한 방법으로 수행하였으며, 흰색의 고체인 N-(4-*tert*-부틸벤질)-N-히드록시-N-[2-플루오로

<189> -4-(메틸술포닐아미노)벤질]티오우레아 화합물(33) (수율 96%)을 수득하였다(표 1 참조).

<190> 녹는점: 136-137 ℃

<191> ^{1}H-NMR($CDCl_3$) δ: 7.44 (t, 1 H, J = 8.3 Hz), 7.38 (AB q, 4 H), 7.01 (dd, 1 H, J = 11.2, 2.2 Hz), 6.86 (dd, 1 H, J = 8.3, 2.2 Hz), 6.52 (s, 1 H, $NHSO_2$), 5.75 (s, 1 H, NH), 5.32 (s, 2 H, CH_2NOH), 4.87 (d, 2 H, J = 5.8 Hz, CH_2NH), 3.00 (s, 3 H, SO_2CH_3), 1.31 (s, 9 H, $C(CH_3)_3$).

<192> IR (KBr): 3266, 2962, 1532, 1325, 1148, 1109 cm^{-1}

<193> MS *m/z*: 440 (MH^+)

<194> 실시예 24. N-(4-*tert*-부틸벤질)-N-히드록시-N-[2-클로로-4-(메틸술포닐아미노)벤질]티오우레아 화합물(34) 제조

<195> 상기의 화합물 23과 화합물 3의 혼합물을 사용하여 실시예 17과 동일한 방법으로 수행하였으며, 흰색의 고체인 N-(4-*tert*-부틸벤질)-N-히드록시-N-[2-클로로-4-(메틸술포닐아미노)벤질]티오우레아 화합물(34) (수율 95%)를 수득하였다(표 1 참조).

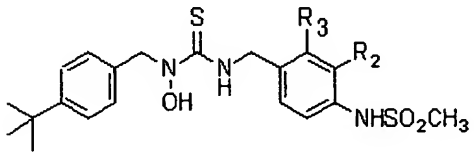
<196> 녹는점: 150-152 ℃

<197> ^{1}H-NMR($CDCl_3$) δ: 7.50 (d, 1 H, *J* = 8.5 Hz), 7.35 (dd, 4 H, *J* = 3.4, 12.2 Hz), 7.29 (d, 1 H, *J* = 2.2 Hz), 7.04 (dd, 1 H, , *J* = 8.3 and 2.2 Hz), 5.32 (s, 2 H, $HONCH_2$), 4.92 (d, 2 H, *J* = 6.1 Hz, $NHCH_2$), 3.02 (s, 3 H, SO_2CH_3), 1.31 (s, 9 H, $C(CH_3)_3$)

<198> IR (KBr): 3400, 2919, 1737, 1383, 1216, 1107 cm^{-1}

<199> MS *m/z*: 456 (MH^+)

<200> 【화학식 10】



(VII)

<201> 【표 1】

화합물군	화합물	R_2	R_3	수율(%)	스펙트럼 데이터
III	28	H	H	94	^{1}H NMR ($CDCl_3$) δ 7.38 (s, 4 H), 7.32 (d, 2 H, J = 8.3 Hz), 7.15 (d, 2 H, J = 8.3 Hz), 6.46 (s, 1 H, $NHSO_2$), 5.97 (bs, 1 H, NHCS), 5.34 (s, 2 H, CH_2NOH), 4.82 (d, 2 H, J = 5.6 Hz, $NHCH_2$), 2.97 (s, 3 H, SO_2CH_3), 1.31 (s, 9 H, $C(CH_3)_3$).

<202>

화합물군	화합물	R_2	R_3	수율(%)	스펙트럼 데이터
III	29	OCH_3	H	92	^1H NMR ($CDCl_3$) δ 7.39 (m, 4 H), 6.99 (m, 1 H), 6.91 (m, 1 H), 6.74 (m, 1 H), 5.52 (bs, 1 H, NH), 5.36 (s, 2 H, CH_2NHOH), 4.83 (d, 2 H, J = 5.6 Hz, CH_2NH), 3.88 (s, 3 H, OCH_3), 2.94 (s, 3 H, SO_2CH_3), 1.32 (s, 9 H, $C(CH_3)_3$)
	30	F	H	93	^1H NMR ($CDCl_3$) δ 7.50 (t, 1 H, J = 8.0 Hz), 7.38 (AB q, 4 H, J = 8.8 Hz),7.1-7.2 (m, 2 H), 5.34 (s, 2 H, CH_2NOH), 4.85 (d, 2 H, J = 5.6 Hz, CH_2NH), 3.00 (s, 3 H, SO_2CH_3), 1.32 (s, 9 H, $C(CH_3)_3$).
	31	Cl	H	91	^1H NMR ($CDCl_3$) δ 7.62 (d, 1 H, *J* = 8.5 Hz), 7.44 (d, 1 H, *J* = 2.0 Hz), 7.36-7.42 (m, 3 H), 7.26 (m, 2 H), 5.36 (s, 2 H, $HONCH_2$), 4.86 (d, 2 H, *J* = 5.8 Hz, $NHCH_2$), 3.01 (s, 3 H, SO_2CH_3), 1.32 (s, 9 H, $C(CH_3)_3$).
	32	NO_2	H	90	^1H NMR ($CDCl_3$) δ 8.22 (d, 1 H, *J* = 2.0 Hz, ArH-2), 7.86 (d, 1 H, *J* = 8.3 Hz, ArH-5), 7.70 (dd, 1 H, *J* = 2.0, 8.3 Hz, ArH-6), 7.40 (dd, 4 H, Ar), 5.36 (s, 2 H, $HONCH_2$), 4.92 (d, 2 H, *J* = 5.6 Hz, $NHCH_2$), 3.14 (s, 3 H, SO_2CH_3), 1.32 (s, 9 H, $C(CH_3)_3$)
	33	H	F	96	^1H NMR ($CDCl_3$) δ 7.44 (t, 1 H, *J* = 8.3 Hz), 7.38 (AB q, 4 H), 7.01 (dd, 1 H, *J* = 11.2, 2.2 Hz), 6.86 (dd, 1 H, *J* = 8.3, 2.2 Hz), 6.52 (s, 1 H, $NHSO_2$), 5.75 (s, 1 H, NH), 5.32 (s, 2 H, CH_2NOH), 4.87 (d, 2 H, *J* = 5.8 Hz, CH_2NH), 3.00 (s, 3 H, SO_2CH_3), 1.31 (s, 9 H, $C(CH_3)_3$).
	34	H	Cl	95	^1H NMR ($CDCl_3$) δ 7.50 (d, 1 H, *J* = 8.5 Hz), 7.35 (dd, 4 H, *J* = 3.4, 12.2 Hz), 7.29 (d, 1 H, *J* = 2.2 Hz), 7.04 (dd, 1 H, , *J* = 8.3 and 2.2 Hz), 5.32 (s, 2 H, $HONCH_2$), 4.92 (d, 2 H, *J* = 6.1 Hz, $NHCH_2$), 3.02 (s, 3 H, SO_2CH_3), 1.31 (s, 9 H, $C(CH_3)_3$)

<203> 실시예 25. N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[4-(메틸술포닐아미노)벤질]티오우레아 화합물(35) 제조

<204> 상기의 화합물 17과 화합물 8의 혼합물을 사용하여 실시예 17과 동일한 방법으로 수행하였으며, 흰색의 고체인 N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[4-(메틸술포닐아미노)벤질]티오우레아 화합물(35) (수율 94%)를 수득하였다(표 2 참조).

<205> 녹는점: 120-123 ℃

<206> ^{1}H-NMR($CDCl_3$) δ: 7.63 (bs, 1 H, NH), 7.28 (d, 2 H, J = 8.3 Hz), 7.15 (d, 2 H, J = 8.3 Hz), 6.8-7.1 (m, 4 H, Ph and NH), 4.74 (d, 2 H, J = 5.6 Hz, $NHCH_2Ar$), 3.95-4.25 (m, 4 H, CH_2OCO, CH_2NOH), 2.96 (s, 3 H, SO_2CH_3), 2.5-2.75 (m, 3 H, $CHCH_2Ar$), 2.24 (d, 6 H, 2 x CH_3), 1.20 (s, 9 H, $C(CH_3)_3$)

<207> IR (KBr): 3266, 1698, 1539, 1337, 1154 cm^{-1}

<208> Mass m/z: 536 (MH^+)

<209> 실시예 26. N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[3-메톡시-4-(메틸술포닐아미노)벤질]티오우레아 화합물(36) 제조

<210> 상기의 화합물 18과 화합물 8의 혼합물을 사용하여 실시예 17과 동일한 방법으로 수행하였으며, 무색의 오일인 N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[3-메톡시-4-(메틸술포닐아미노)벤질]티오우레아 화합물(36) (수율 90%)을 수득하였다(표 2 참조).

<211> ^{1}H-NMR($CDCl_3$) δ: 7.47 (d, 1 H, J = 8.0 Hz), 6.88-7.06 (m, 5 H), 6.74 (s, 1 H, $NHSO_2$), 4.77 (d, 2 H, CH_2NOH), 4.1-4.25 (m, 3 H, CH_2NH and CH_2OCO), 4.00 (AB q, 1 H, J = 5.4 Hz,

CH_2OCO), 3.87 (s, 3 H, OCH3), 2.94 (s, 3 H, SO_2CH_3), 2.5-2.7 (m, 3 H, CH_2Ar and CH), 2.2-2.3 (m, 6 H, 2 x CH_3), 1.18 (s, 9 H, $C(CH_3)_3$).

<212> IR (KBr): 3334, 2921, 1716 cm^{-1}

<213> MS *m/z*: 566 (MH^+)

<214> 실시예 27. N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[3-플루오로-4-(메틸술포닐아미노)벤질]티오우레아 화합물 (37) 제조

<215> 상기의 화합물 19와 화합물 8의 혼합물을 사용하여 실시예 17과 동일한 방법으로 수행하였으며, 흰색의 고체인 N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[3-플루오로-4-(메틸술포닐아미노)벤질]티오우레아 화합물 (37) (수율 93%)을 수득하였다(표 2 참조).

<216> 녹는점: 52-55 ℃

<217> ^1H-NMR($CDCl_3$) δ: 7.74 (bs, 1 H), 7.64 (bs, 1 H), 7.52 (t, 1 H, *J* = 8.3 Hz), 6.9-7.25 (m, 5 H), 6.45 (bs, 1 H, $NHSO_2$), 4.81 (d, 2 H, *J* = 3.7 Hz, $NHCH_2Ar$), 4.18 (m, 3 H, CH_2 NOH and CH_2OCO), 4.00 (dd, 1 H, CH_2OCO), 3.01 (s, 3 H, SO_2CH_3), 2.5-2.8 (m, 3 H, $CHCH_2$ Ph), 2.2-2.3 (m, 6 H, 2 x CH_3), 1.19 (s, 9 H, $C(CH_3)_3$)

<218> IR (KBr): 3362, 2971, 1715, 1508, 1337, 1158 cm^{-1}

<219> MS *m/z*: 554 (MH^+)

<220> 실시예 28. N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[2-플루오로-4-(메틸술포닐아미노)벤질]티오우레아 화합물 (38) 제조

<221> 상기의 화합물 22와 화합물 8의 혼합물을 사용하여 실시예 17과 동일한 방법으로 수행하였으며, 흰색의 고체인 N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[2-플루오로-4-(메틸술포닐아미노)벤질]티오우레아 화합물 (38) (수율 91%)을 수득하였다(표 2 참조).

<222> 녹는점: 55-57 ℃

<223> ^{1}H-NMR($CDCl_3$) δ: 7.39 (t, 1 H, J = 8.0 Hz), 7.85-7.05 (m, 5 H), 6.9-7.25 (m, 5 H), 4.81 (d, 2 H, J = 5.6 Hz, $NHCH_2Ar$), 3.95-4.25 (m, 4 H, CH_2NOH and CH_2OCO), 3.00 (s, 3 H, SO_2CH_3), 2.5-2.8 (m, 3 H, $CHCH_2Ph$), 2.2-2.3 (m, 6 H, 2 x CH_3), 1.19 (s, 9 H, $C(CH_3)_3$).

<224> IR (KBr): 3254, 2971, 1701, 1626, 1530, 1331, 1149 cm^{-1}

<225> MS *m/z* : 554 (MH^+)

<226> 실시예 29. N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[2-클로로-4-(메틸술포닐아미노)벤질]티오우레아 화합물 (39) 제조

<227> 상기의 화합물 23과 화합물 8의 혼합물을 사용하여 실시예 17과 동일한 방법으로 수행하였으며, 흰색의 고체인 N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[2-클로로-4-(메틸술포닐아미노)벤질]티오우레아 화합물(39) (수율 94%)를 수득하였다(표 2 참조).

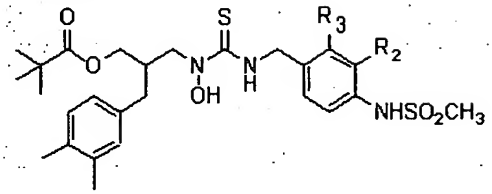
<228> 녹는점: 56-58 ℃

<229> ^{1}H-NMR($CDCl_3$) δ: 7.35-7.45 (m, 2 H), 6.9-7.05 (m, 4 H), 4.85 (d, 2 H, J = 6.1 Hz, $NHCH_2Ar$), 3.95-4.25 (m, 4 H, CH_2NOH and CH_2OCO), 2.99 (s, 3 H, SO_2CH_3), 2.5-2.8 (m, 3 H, $CHCH_2Ph$), 2.2-2.3 (m, 6 H, 2 x CH_3), 1.20 (s, 9 H, $C(CH_3)_3$).

<230> IR (KBr): 3262, 2972, 1698, 1608, 1531, 1325, 1156 cm^{-1}

<231> MS *m/z* : 570(MH^+)

<232> 【화학식 11】



(VIII)

<233> 【표 2】

화합물군	화합물	R_2	R_3	수율(%)	스펙트럼 데이터
III	35	H	H	94	^1H NMR ($CDCl_3$) δ 7.63 (bs, 1 H, NH), 7.28 (d, 2 H, *J* = 8.3 Hz), 7.15 (d, 2 H, *J* = 8.3 Hz), 6.8-7.1 (m, 4 H, Ph and NH), 4.74 (d, 2 H, *J* = 5.6 Hz, $NHCH_2Ar$), 3.95-4.25 (m, 4 H, CH_2OCO, CH_2NOH), 2.96 (s, 3 H, SO_2CH_3), 2.5-2.75 (m, 3 H, $CHCH_2Ar$), 2.24 (d, 6 H, 2 x CH_3), 1.20 (s, 9 H, $C(CH_3)_3$)
	36	OCH_3	H	90	^1H NMR ($CDCl_3$) δ 7.47 (d, 1 H, *J* = 8.0 Hz), 6.88-7.06 (m, 5 H), 6.74 (s, 1 H, $NHSO_2$), 4.77 (d, 2 H, CH_2NOH), 4.1-4.25 (m, 3 H, CH_2NH and CH_2OCO), 4.00 (AB q, 1 H, *J* = 5.4 Hz, CH_2OCO), 3.87 (s, 3 H, OCH3), 2.94 (s, 3 H, SO_2CH_3), 2.5-2.7 (m, 3 H, CH_2Ar and CH), 2.2-2.3 (m, 6 H, 2 x CH_3), 1.18 (s, 9 H, $C(CH_3)_3$).
	37	F	H	93	^1H NMR ($CDCl_3$) δ 7.74 (bs, 1 H), 7.64 (bs, 1 H), 7.52 (t, 1 H, J = 8.3 Hz), 6.9-7.25 (m, 5 H), 6.45 (bs, 1 H, $NHSO_2$), 4.81 (d, 2 H, J = 3.7 Hz, $NHCH_2Ar$), 4.18 (m, 3 H, CH_2NOH and CH_2OCO), 4.00 (dd, 1 H, CH_2OCO), 3.01 (s, 3 H, SO_2CH_3), 2.5-2.8 (m, 3 H, $CHCH_2Ph$), 2.2-2.3 (m, 6 H, 2 x CH_3), 1.19 (s, 9 H, $C(CH_3)_3$)

<234>

화합물군	화합물	R_2	R_3	수율(%)	스펙트럼 데이터
III	38	H	F	91	^{1}H NMR ($CDCl_3$) δ 7.39 (t, 1 H, J = 8.0 Hz), 7.85-7.05 (m, 5 H), 6.9-7.25 (m, 5 H), 4.81 (d, 2 H, J = 5.6 Hz, $NHCH_2Ar$), 3.95-4.25 (m, 4 H, CH_2NOH and CH_2OCO), 3.00 (s, 3 H, SO_2CH_3), 2.5-2.8 (m, 3 H, $CHCH_2Ph$), 2.2-2.3 (m, 6 H, 2 x CH_3), 1.19 (s, 9 H, $C(CH_3)_3$).
	39	H	Cl	94	^{1}H NMR ($CDCl_3$) δ 7.35-7.45 (m, 2 H), 6.9-7.05 (m, 4 H), 4.85 (d, 2 H, J = 6.1 Hz, $NHCH_2Ar$), 3.95-4.25 (m, 4 H, CH_2NOH and CH_2OCO), 2.99 (s, 3 H, SO_2CH_3), 2.5-2.8 (m, 3 H, $CHCH_2Ph$), 2.2-2.3 (m, 6 H, 2 x CH_3), 1.20 (s, 9 H, $C(CH_3)_3$).

<235> 실시예 30. N-[2-(4-*tert*-부틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[4-(메틸술포닐아미노)벤질]티오우레아 화합물(40, SU-552) 제조

<236> 상기의 화합물 17과 화합물 9의 혼합물을 사용하여 실시예 17과 동일한 방법으로 수행하였으며, 흰색의 고체인 N-[2-(4-*tert*-부틸벤질)-3-(피발로올옥시)프로필]-N-히드록시-N-[4-(메틸술포닐아미노)벤질]티오우레아 화합물(40, SU-552) (수율 97%)을 수득하였다(표 3 참조).

<237> 녹는점: 149-150 ℃

<238> ^{1}H-NMR($CDCl_3$) δ: 7.79 (bs, 1 H, OH), 7.25-7.32 (m, 4 H), 7.1-7.18 (m, 4 H, Ar), 6.91 (bs, 1 H, $NHSO_2$), 4.75 (d, 2 H, J = 5.5 Hz, $NHCH_2Ar$), 4.29 (dd of AB, 1 H, J = 10.3, 14.5 Hz, CH_2NOH), 4.12 (m, 2 H, CH_2OCO), 3.98 (dd of AB, 1 H, J = 5, 14.5 Hz, CH_2NOH), 2.96 (s, 3 H, SO_2CH_3), 2.69 (d, 2 H, J = 7 Hz, CH_2Ar), 2.59 (bs, 1 H, CH), 1.29 (s, 9 H, $C(CH_3)_3$), 1.16 (s, 9 H, $C(CH_3)_3$).

<239> IR (KBr): 3295, 3186, 2964, 1706, 1529, 1321, 1184, 1147 cm^{-1}

<240> MS *m/z* : 564(MH^+)

<241> 실시예 31. N-[2-(4-*tert*-부틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[3-플루오로-4-(메틸술포닐아미노)벤질]티오우레아 화합물(41) 제조

<242> 상기의 화합물 19와 화합물 9의 혼합물을 사용하여 실시예 17과 동일한 방법으로 수행하였으며, 흰색의 고체인 N-[2-(4-*tert*-부틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[3-플루오로-4-(메틸술포닐아미노)벤질]티오우레아 화합물(41) (수율 95%)을 수득하였다(표 3 참조).

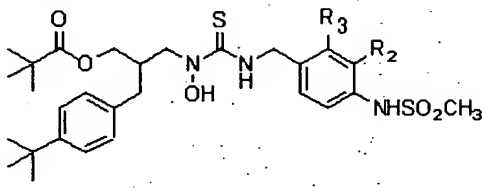
<243> 녹는점: 128-129 ℃

<244> ^{1}H-NMR($CDCl_3$) δ: 7.83 (bs, 1 H), 7.49 (t, 1 H, *J* = 8.0 Hz), 7.31 (d, 2 H, *J* = 8.3 Hz), 7.05-7.2 (m, 3 H), 6.60 (bs, 1 H, $NHSO_2$), 4.79 (m, 2 H, $NHCH_2Ar$), 4.29 (dd, 1 H, CH_2 OCO), 4.05-4.20 (m, 2 H, CH2NOH), 3.97 (dd, 1 H, CH_2OCO), 3.00 (s, 3 H, SO_2CH_3), 2.69 (d, 2 H, *J* = 7.1 Hz, CH_2Ar), 2.58 (bs, 1 H, CH), 1.29 (s, 9 H, $C(CH_3)_3$), 1.16 (s, 9 H, $C(CH_3)_3$).

<245> IR (KBr): 3244, 2964, 1716, 1509, 1331, 1158 cm^{-1}

<246> MS *m/z* : 582 (MH^+)

<247> 【화학식 12】



(IX)

<248> 【표 3】

화합물군	화합물	R_2	R_3	수율(%)	스펙트럼 데이터
III	40	H	H	97	^{1}H NMR ($CDCl_3$) δ 7.79 (bs, 1 H, OH), 7.25-7.32 (m, 4 H), 7.1-7.18 (m, 4 H, Ar), 6.91 (bs, 1 H, $NHSO_2$), 4.75 (d, 2 H, J = 5.5 Hz, $NHCH_2Ar$), 4.29 (dd of AB, 1 H, J = 10.3, 14.5 Hz, CH_2 NOH), 4.12 (m, 2 H, CH_2OCO), 3.98 (dd of AB, 1 H, J = 5, 14.5 Hz, CH_2NOH), 2.96 (s, 3 H, SO_2CH_3), 2.69 (d, 2 H, J = 7 Hz, CH_2Ar), 2.59 (bs, 1 H, CH), 1.29 (s, 9 H, $C(CH_3)_3$), 1.16 (s, 9 H, $C(CH_3)_3$).
	41	F	H	95	^{1}H NMR ($CDCl_3$) δ 7.83 (bs, 1 H), 7.49 (t, 1 H, J = 8.0 Hz), 7.31 (d, 2 H, J = 8.3 Hz), 7.05-7.2 (m, 3 H), 6.60 (bs, 1 H, $NHSO_2$), 4.79 (m, 2 H, $NHCH_2Ar$), 4.29 (dd, 1 H, CH_2OCO), 4.05-4.20 (m, 2 H, CH2NOH), 3.97 (dd, 1 H, CH_2 OCO), 3.00 (s, 3 H, SO_2CH_3), 2.69 (d, 2 H, J = 7.1 Hz, CH_2Ar), 2.58 (bs, 1 H, CH), 1.29 (s, 9 H, $C(CH_3)_3$), 1.16 (s, 9 H, $C(CH_3)_3$).

<249> 실시예 32. 4-(메틸술포닐아미노)페닐아세트산 화합물(43) 제조

<250> 4-아미노페닐아세트산 1g(6.66 mmol)을 녹인 THF 10㎖에 1N 수산화나트륨을 pH 9가 될 때까지 적가한 후, 1시간동안 메탄술포닐 클로라이드 0.77㎖(9.99 mmol)이 용해된 THF 10㎖을 한 방울씩 떨어뜨리면서 반응을 시키고, 혼합물은 1N 염산으로 pH 3이 될 때까지 산성화시키고

, 물로 희석한 후, 수회동안 에틸아세테이트로 추출하였다. 유기층을 물로 세척한 후, 황산마그네슘을 이용하여 건조하고 진공상태에서 농축하였으며, 잔사물은 컬럼 크로마토그래피(전개용매: 에틸아세테이트/헥산=2:3)로 분리 및 정제하여 노랑색의 고체인 4-(메틸술포닐아미노)페닐아세트산 화합물(43) 0.855g(수율 56%)를 수득하였다.

<251> ^{1}H-NMR(DMSO-d_6) δ : 9.67 (s, 1 H, COOH), 7.20 (d, 2 H, J = 8.5 Hz, Ar), 7.13 (d, 2 H, J = 8.5 Hz, Ar), 3.50 (s, 2 H, CH_2), 3.95 (s, 3 H, SO_2CH_3)

<252> 실시예 33. 펜타플루오로페닐 2-[4-(메틸술포닐아미노)페닐]아세테이트 화합물

<253> (44) 제조

<254> 펜타플루오로 페놀 0.607g(3.3 mmol)과 디메틸아미노피리딘 0.036g(0.3mmol)이 용해된 디클로로메탄 15㎖의 0℃의 냉각 혼합물에 디사이클로렉실카보이미드 1.0M 4.5㎖를 한 방울씩 적가하여 반응을 시켜 실온에서 16시간 저어주었다. 반응 혼합물은 감압농축하였으며, 에테르로 희석한 후 여과하였고, 여과액을 감압농축하였다. 잔사물은 컬럼 크로마토그래피(전개용매: 에틸아세테이트/헥산=1:10)으로 분리 및 정제하여, 흰색의 고체인 펜타플루오로페닐 2-[4-(메틸술포닐아미노)페닐]아세테이트 화합물(44) 0.592g(수율 50%)을 수득하였다.

<255> ^{1}H-NMR($CDCl_3$) δ : 7.36 (d, 2 H, J = 8.5 Hz, Ar), 7.24 (d, 2 H, J = 8.5 Hz, Ar), 3.96 (s, 2 H, CH_2), 3.03 (s, 3 H, SO_2CH_3).

<256> 실시예 34. N-(4-*tert*-부틸벤질)-N-히드록시-[4-(메틸술포닐아미노)페닐]아세트아미드 화합물(45) 제조

<257> 상기의 화합물 44와 화합물 3의 혼합물을 축합하여 실시예 33과 동일한 방법으로 수행하였으며, 흰색의 고체인 N-(4-*tert*-부틸벤질)-N-히드록시-[4-(메틸술포닐아미노)페닐]아세트아미드 화합물(45) (수율 47%)을 수득하였다(표 4 참조).

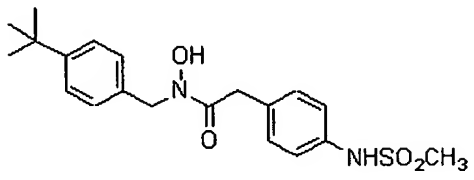
<258> 녹는점: 161-163 ℃

<259> ^{1}H-NMR(acetone-d_6) δ : 9.02 (bs, 1 H, OH), 8.48 (bs, 1 H, $NHSO_2$), 7.2-7.4 (m, 8 H, Ar), 4.75 (s, 2 H, CH_2NOH), 3.82 (s, 2 H, CH_2CO), 2.95 (s, 3 H, SO_2CH_3), 1.29 (s, 9 H, $C(CH_3)_3$).

<260> IR (KBr): 3350, 1650, 1515, 1338, 1154 cm^{-1}

<261> MS *m/z* : 391 (MH^+)

<262> 【화학식 13】



<263>

【표 4】

화합물군	화합물	수율(%)	스펙트럼 데이터
IV	45	47	^{1}H NMR (acetone-d_6) δ 9.02 (bs, 1 H, OH), 8.48 (bs, 1 H, $NHSO_2$), 7.2-7.4 (m, 8 H, Ar), 4.75 (s, 2 H, CH_2NOH), 3.82 (s, 2 H, CH_2CO), 2.95 (s, 3 H, SO_2CH_3), 1.29 (s, 9 H, $C(CH_3)_3$).

<264> 실시예 35. *tert*-부틸 N-[(*tert*-부톡시카보닐)옥시]-N-(4-니트로벤질)카바메이트 화합물(47) 제조

<265> 4-니트로벤질 브로마이드를 출발물질로 하여 *tert*-부틸-N-(*tert*-부톡시카보닐옥시)카바메이트와 염기조건하에서 반응하였으며, 무색의 오일인 *tert*-부틸 N-[(*tert*-부톡시카보닐)옥시]-N-(4-니트로벤질)카바메이트 화합물(47) (수율 81%)를 수득하였다.

<266> ^{1}H-NMR($CDCl_3$) δ : 8.14 (dt, 2 H, J = 2.2, 8.6 Hz, Ar), 7.48 (d, 2 H, J = 8.6 Hz, Ar), 4.81 (s, 2H, CH_2), 1.44 (bs, 18 H, 2 x $C(CH_3)_3$).

<267> 실시예 36. *tert*-부틸 N-[(*tert*-부톡시카보닐)옥시]-N-[4-(메틸술포닐아미노)벤질] 카바메이트 화합물(48) 제조

<268> 상기 실시예 35의 *tert*-부틸 N-[(*tert*-부톡시카보닐)옥시]-N-(4-니트로벤질)카바메이트 화합물(47)의 부유물 6.40g(17.3mmol)과 Pd-C 650mg을 메탄올 100㎖에 넣고 수소 조건하에서 2시간동안 수소화반응을 하였다. 반응 혼합물을 여과하고, 여과물은 감압농축하였으며, 잔사물은 피리딘 60㎖에 용해한 후, 메탄술포닐클로라이드 20.1㎖(26.0mmol)을 처리하였고, 실온에서

3시간 저어준 후, 물로 희석시키고, 수회 동안 에틸아세테이트로 추출하였다. 유기층을 물과 생리식염수로 세척하고, 황산나트륨으로 건조하고 감압농축하였으며, 잔사물은 컬럼 크로마토그래피(전개용매: 에틸아세테이트/헥산=2:3)으로 분리 및 정제하여 점성의 시럽형태인 *tert*-부틸 N-[(*tert*-부톡시카보닐)옥시]-N-[4-(메틸술포닐아미노)벤질] 카바메이트 화합물(48) 6.56g(수율 91%)을 수득하였다.

<269> ^{1}H-NMR($CDCl_3$) δ : 7.32 (d, 2 H, J = 8.6 Hz, Ar), 7.20 (dd, 2 H, J = 1.7, 8.6 Hz, Ar), 4.72 (s, 2 H, CH_2), 2.99 (s, 3 H, SO_2CH_3), 1.48 (bs, 18 H, 2 x $C(CH_3)_3$).

<270> 실시예 37. N-[4-(메틸술포닐아미노)벤질]히드록실아민 화합물(49) 제조

<271> 상기 실시예 36의 *tert*-부틸 N-[(*tert*-부톡시카보닐)옥시]-N-[4-(메틸술포닐아미노)벤질] 카바메이트 화합물(48) 6.56g(15.7mmol)을 0℃에서 냉각된 트리플루오로아세트산 30mℓ로 처리하였으며, 반응 혼합물은 실온에서 20분동안 저어준 후, 감압농축하여 노란색 고체인 N-[4-(메틸술포닐아미노)벤질]히드록실아민 화합물(49) 5.19g(수율 100%)를 수득하였다.

<272> ^{1}H-NMR(DMSO-d_6) δ : 11.26 (bs, 1 H), 10.8 (bs, 1 H), 9.87 (s, 1 H), 7.34 (d, 2 H, J = 8.5 Hz, Ar), 7.15 (dd, 2 H, J = 8.5 Hz, Ar), 4.19 (s, 2 H, CH_2), 2.94 (s, 3 H, SO_2CH_3).

<273> 실시예 38. 벤질 N-(2-플루오로-4-메틸페닐)카바메이트 화합물(51) 제조

<274> 2-플루오로-4-메틸아닐린 화합물(50) 400mg(3.2mmol)을 피리딘 4mℓ에 용해시키고, 0℃에서 벤질클로로포메이트 0.68mℓ(4.8mmol)을 한방울씩 적가하여 반응을 하였으며, 반응 혼합물은

0℃에서 20분간 저어준 후, 에탄올 0.2㎖로 반응을 종료하였다. 물로 희석하여 여과한 후, 잔사물은 컬럼 크로마토그래피(전개용매: 에틸아세테이트/헥산=1:10)로 분리 및 정제하여 엷은 분홍색의 고체인 벤질 N-(2-플루오로-4-메틸페닐)카바메이트 화합물(51) 730mg(수율 88%)을 수득하였다.

<275> 녹는점: 66 ℃

<276> ^{1}H-NMR($CDCl_3$) δ : 7.93 (bt, 1 H), 7.3-7.45 (m, 5 H, Ph), 6.86-6.93 (m, 2 H), 6.80 (bs, 1 H, NH), 5.21 (s, 2 H, OCH_2Ph), 2.30 (s, 3 H, CH_3).

<277> 실시예 39. 벤질 N-[4-(브로모메틸)-2-플루오로페닐)카바메이트 화합물(52) 제조

<278> 벤질 N-(2-플루오로-4-메틸페닐)카바메이트 화합물(51) 500mg이 용해된 디클로로메탄 8㎖ 용액에 NBS 360mg(2.02mmol)과 촉매로 AIBN을 처리하고, 반응 혼합물은 300와트 할로겐 램프하에서 2시간 30분정도 환류추출하였으며, 실온에서 냉각하여 탈수하였다. 잔사물은 컬럼 크로마토그래피(전개용매:에틸아세테이트/헥산 =

<279> 1:10)로 분리 및 정제하여 진한 회색 고체인 벤질 N-[4-(브로모메틸)-2-플루오로페닐)카바메이트 화합물(52) 268mg(수율 41%)를 수득하였다.

<280> 녹는점 : 95-96 ℃

<281> ^{1}H-NMR ($CDCl_3$) δ : 8.10 (bt, 1 H, J = 8.4 Hz), 7.35-7.45 (m, 5 H, Ph), 7.10-7.16 (m, 2 H), 6.94 (bs, 1 H, NH), 5.22 (s, 2 H, OCH_2Ph), 4.43 (s, 2 H, CH_2Br)

<282> 실시예 40. *tert*-부틸 N-[(*tert*-부톡시카보닐)옥시]-N-{4-[(벤질옥시)카보닐아미노]-3-플루오로벤질}카바메이트 화합물(53) 제조

<283> *tert*-부틸-N-(*tert*-부톡시카보닐옥시)카바메이트 224mg(0.96 mmol)이 용해된 DMF 2mℓ에 용해된 용액에 수소화나트륨 38mg(0.96mmol)을 0℃에서 반응하여 실온에서 20분동안 저어주었으며, 디클로로메탄에 용해된 벤질 N-[4-(브로모메틸)-2-플루오로페닐)카바메이트 화합물(52) 250mg(0.74mmol)을 한방울씩 첨가한 후, 1시간동안 저어주었다. 농축후, 잔존하는 혼합물은 컬럼 크로마토그래피(전개용매:에틸아세테이트/헥산=1:5)로 분리 및 정제하여 노란 오일의 *tert*-부틸 N-[(*tert*-부톡시카보닐)옥시]-N-{4-[(벤질옥시)카보닐아미노]-3-플루오로벤질}카바메이트 화합물(53) 355mg(수율 98%)을 수득하였다.

<284> ^{1}H-NMR($CDCl_3$) δ : 8.06 (bt, 1 H), 7.35-7.45 (m, 5 H, Ph), 7.05-7.12 (m, 2 H), 6.89 (bs, 1 H, NH), 5.22 (s, 2 H, OCH_2Ph), 4.68 (s, 2 H, CH_2NO), 1.48 (s, 9 H, $C(CH_3)_3$), 1.47 (s, 9 H, $C(CH_3)_3$)

<285> 실시예 41. *tert*-부틸 N-(4-아미노-3-플루오로벤질)-N-[(*tert*-부톡시카보닐)옥시]카바메이트 화합물(54) 제조

<286> *tert*-부틸 N-[(*tert*-부톡시카보닐)옥시]-N-{4-[(벤질옥시)카보닐아미노]-3-플루오로벤질}카바메이트 화합물(53) 350mg(0.714mmol)과 10% Pd-C 35mg을 메탄올 8mℓ에 용해시키고, 실온에서 1시간동안 수소조건하에서 수소화 반응을 하였으며, 여과 후, 여과물은 감압농축하였고, 잔사물은 헥산을 사용하여 결정화하여 아이보리색의 고체인 *tert*-부틸 N-(4-아미노-3-플루오로벤질)-N-[(*tert*-부톡시카보닐)옥시]카바메이트 화합물(54) 232mg(수율 91%)을 수득하였다.

<287> 녹는점 : 105-106 ℃

<288> ^{1}H-NMR($CDCl_3$) δ : 6.99 (dd, 1 H, *J* = 1.6, 12 Hz), 6.90 (dd, 1 H, *J* = 1.6, 8.1 Hz), 6.71 (t, 1 H, *J* = 8.8 Hz), 4.61 (s, 2 H, CH_2NO), 3.70 (bs, 2 H, NH_2), 1.48 (s, 9 H, $C(CH_3)_3$), 1.47 (s, 9 H, $C(CH_3)_3$)

<289> 실시예 42. *tert*-부틸 N-[(*tert*-부톡시카보닐)옥시]-N-[3-플루오로-4-(메틸술포닐아미노)벤질]카바메이트 화합물(55, SU-576) 제조

<290> *tert*-부틸-N-(4-아미노-3-플루오로벤질)-N-[(*tert*-부톡시카보닐)옥시]카바메이트 화합물(54) 210mg(0.59mmol)이 용해된 냉각된 피리딘 2㎖ 용액에 메탄술포닐클로라이드 0.09㎖(1.178mmol)을 한방울씩 적가하였으며, 0℃에서 30분 동안 저어주었다. 반응 혼합물은 컬럼 크로마토그래피(전개용매:에틸아세테이트/헥산=1:2)로 분리 및 정제하여 헥산과 디에틸에스테르로 결정화하여 *tert*-부틸-N-[(*tert*-부톡시카보닐)옥시]-N-[3-플루오로-4-(메틸술포닐아미노)벤질]카바메이트 화합물(55, SU-576) 238mg(수율 93%)을 수득하였다.

<291> 녹는점: 112 - 113 ℃

<292> ^{1}H-NMR ($CDCl_3$) δ : 7.53(t, 1 H, *J* = 8.25 Hz), 7.12-7.2(m, 2 H), 6.90(bs, 1 H, NH), 4.73(s, 2 H, CH_2NO), 3.02(s, 3 H, SO_2CH_3), 1.49 s, 18 H)

<293> 실시예 43. N-[3-플루오로-4-(메틸술포닐아미노)벤질]히드록실아민 화합물(56) 제조

<294> *tert*-부틸-N-[(*tert*-부톡시카보닐)옥시]-N-[3-플루오로-4-(메틸술포닐아미노)벤질]카바메이트 화합물(55, SU-576) 225㎎(0.518㎖)이 용해된 디클로로메탄 10㎖ 냉각 용액에 삼불화아세트산 2㎖를 0℃에서 적가하여 실온에서 50분동안 저어주었다. 혼합물은 실온 이하에서 탈수하였으며, 진공펌프로 농축하였고, 잔사물은 에틸아세트로 용해하여 수회 동안 포화된 탄산수소나트륨으로 세척하였다. 유기층은 황산마그네슘으로 건조하고 감압농축하여 오일형태인 N-[3-플루오로-4-(메틸술포닐아미노)벤질]히드록실아민 화합물(56)을 수득하였다.

<295> ^{1}H-NMR($CDCl_3$) δ : 7.56 (m, 1 H), 7.1-7.3 (m, 2 H), 7.02 (bs, 1 H, $NHSO_2$), 4.85 (s, 2 H, CH_2NOH), 2.94 (s, 3 H, SO_2CH_3).

<296> 실시예 44. 4-(*tert*-부틸벤질)이소티오시아네이트 화합물(57) 제조

<297> 4-*tert*-부틸벤질아민 1g(6.13㎜ol)과 트리에틸아민 1.29㎖(9.20㎜ol)이 용해된 디클로로메탄 20㎖ 냉각 혼합 용액에 1,1-티오-디-2-피리돈 1.42g(6.13㎜ol)을 0℃에서 넣어 반응하였으며, 실온에서 20분간 저어주고, 감압농축하였다. 잔사물은 컬럼 크로마토그래피(전개용매: 에틸아세테이트/헥산=1:10)로 분리 및 정제하여 흰색의 고체인 4-(*tert*-부틸벤질)이소티오시아네이트 화합물(57) 0.755g(수율 60%)을 수득하였다.

<298> 녹는점: 47.3 ℃

<299> ^{1}H-NMR($CDCl_3$) δ : 7.40 (dt, 2 H, J = 2.2, 8.6 Hz, Ar), 7.24 (d, 2 H, J = 8.6 Hz, Ar), 4.67 (s, 2 H, CH_2), 1.32 (s, 9 H, $C(CH_3)_3$).

<300> 실시예 45. 4-(*tert*-부틸벤질)이소티오시아네이트 화합물(58) 제조

<301> 4-*tert*-부틸벤질아민 1g(6.13 mmol)이 용해된 톨루엔 10㎖ 용액에 트리포스겐 2.48g(9.20mmol)로 반응하였으며, 반응 혼합물은 100℃에서 20분간 환류추출하여 감압농축하였다. 잔사물은 컬럼 크로마토그래피(전개용매: 에틸아세테이트/헥산=1:10)로 분리 및 정제하여 무색의 오일인 4-(*tert*-부틸벤질)이소티오시아네이트 화합물(58) 0.859g(수율 74%)을 수득하였다.

<302> ^{1}H-NMR($CDCl_3$) δ : 7.39 (dt, 2 H, J = 2.2, 8.6 Hz, Ar), 7.23 (d, 2 H, J = 8.6 Hz, Ar), 4.43 (s, 2 H, CH_2), 1.31 (s, 9 H, $C(CH_3)_3$).

<303> 실시예 46. 펜타플로로페닐 2-(4-*tert*-부틸페닐)아세테이트 화합물(59) 제조

<304> (4-*tert*-부틸페닐)아세트산 1g(5.20 mmol), 펜타플로로페놀 1.15g(6.24 mmol)과 촉매인 디메틸아미노피리딘이 용해된 디클로로메탄 30㎖ 냉각 혼합 용액에 디사이클로헥실카보디이미드 1.0M 용액 6.24㎖(6.24mmol)를 0℃에서 넣어 실온에서 16시간동안 저어주었으며, 반응 혼합물은 감압농축하여 에테르로 희석하고 여과한 후, 여과물은 감압농축하였다. 잔사물은 컬럼 크로마토그래피(전개용매: 에틸아세테이트/헥산=1:10)로 분리 및 정제하여, 무색의 오일인 펜타플로로페닐 2-(4-*tert*-부틸페닐)아세테이트 화합물(59) 1.86g(수율 100%)을 수득하였다.

<305> ^{1}H-NMR($CDCl_3$) δ : 7.40 (dt, 2 H, J = 2.2, 8.3 Hz, Ar), 7.28 (d, 2 H, J = 8.3 Hz, Ar), 3.94 (s, 2 H, CH_2), 1.32 (s, 9 H, $C(CH_3)_3$).

<306> 실시예 47. N-(4-*tert*-부틸벤질)-N-히드록시-N-[4-(메틸술포닐아미노)벤질]티오우레아 화합물(60) 제조

<307> N-[4-(메틸술포닐아미노)벤질]히드록실아민 화합물(49) 165㎎(0.5mmol)과 디이소프로필에틸아민 0.13㎖(0.75 mmol)를 DMF 3 ㎖에 넣고 1시간동안 실온에서 저어주었으며, 혼합물은 상기의 화합물 57(0.5 mmol)을 넣어주고 실온에서 20시간동안 저어주었다. 반응 혼합물은 물로 희석하였으며, 수회동안 에틸아세테이트로 추출한 후, 유기층은 물로 세척하고 황산마그네슘으로 건조하며, 감압농축하였다. 잔사물은 컬럼 크로마토그래피(전개용매:에틸아세테이트/헥산=2:1)로 분리 및 정제하여 흰색 고체인 N-(4-*tert*-부틸벤질)-N-히드록시-N-[4-(메틸술포닐아미노)벤질]티오우레아 화합물(60) (수율:90%)을 수득하였다(표 5 참조).

<308> 녹는점: 124 ℃

<309> ^{1}H-NMR(acetone-d_6) δ: 8.77 (bs, 1 H, N-OH), 8.22 (t, 1 H, J = 6.0 Hz, NHCS), 7.25-7.45 (m, 8 H), 5.34 (s, 2 H, HONCH_2Ar), 4.84 (d, 2 H, J = 6.0 Hz, ArCH_2NH), 2.97 (s, 3 H, SO_2CH_3), 1.29 (s, 9 H, C(CH_3)$_3$).

<310> MS *m/z* : 422 (MH^+)

<311> 실시예 48. N-(4-*tert*-부틸벤질)-N-히드록시-N-[4-(메틸술포닐아미노)벤질]우레아 화합물(62) 제조

<312> N-[4-(메틸술포닐아미노)벤질]히드록실아민 화합물(49) 165㎎(0.5mmol)과 디이소프로필에틸아민 0.13㎖(0.75 mmol)를 DMF 3 ㎖에 넣고 1시간동안 실온에서 저어주었으며, 혼합물은 상기의 화합물 58(0.5 mmol)을 넣어주고 실온에서 20시간동안 저어주었다. 반응 혼합물은 물로 희석하였으며, 수회동안 에틸아세테이트로 추출한 후, 유기층은 물로 세척하고 황산마그네슘으로 건조하며, 감압농축하였다. 잔사물은 컬럼 크로마토그래피(전개용매:에틸아세테이트/헥산

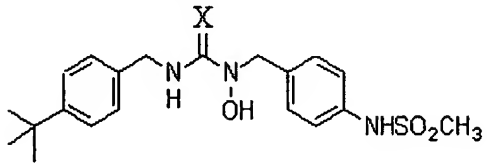
=2:1)로 분리 및 정제하여 흰색 고체인 N-(4-*tert*-부틸벤질)-N-히드록시-N-[4-(메틸술포닐아미노)벤질]우레아 화합물(62)(수율 74%)을 수득하였다(표 5 참조).

<313> 녹는점: 125 ℃

<314> ^{1}H-NMR ($CDCl_3$) δ 7.32 (d, 2 H, J = 8.3 Hz), 7.27 (d, 2 H, J = 8.3 Hz), 7.18 (d, 2 H, J = 8.3 Hz), 7.10 (d, 2 H, J = 8.3 Hz), 6.76 (bs, 1 H, NH), 6.69 (bs, 1 H, OH), 6.29 (t, 1 H, J = 5.8 Hz, NH), 4.59 (s, 2 H, $HONCH_2Ar$), 4.36 (d, 2 H, J = 5.8 Hz, $ArCH_2NH$), 2.96 (s, 3 H, SO_2CH_3), 1.29 (s, 9 H, $C(CH_3)_3$).

<315> MS m/z :406 (MH^+)

<316> 【화학식 14】



(X)

<317>

【표 5】

화합물군	화합물	X	수율(%)	스펙트럼 데이터
V	60	S	80	^{1}H NMR (acetone-d_6) δ 8.77 (bs, 1 H, N-OH), 8.22 (t, 1 H, J = 6.0 Hz, NHCS), 7.25-7.45 (m, 8 H), 5.34 (s, 2 H, $HONCH_2Ar$), 4.84 (d, 2 H, J = 6.0 Hz, $ArCH_2NH$), 2.97 (s, 3 H, SO_2CH_3), 1.29 (s, 9 H, $C(CH_3)_3$).
	62	O	74	^{1}H NMR ($CDCl_3$) δ 7.32 (d, 2 H, J = 8.3 Hz), 7.27 (d, 2 H, J = 8.3 Hz), 7.18 (d, 2 H, J = 8.3 Hz), 7.10 (d, 2 H, J = 8.3 Hz), 6.76 (bs, 1 H, NH), 6.69 (bs, 1 H, OH), 6.29 (t, 1 H, J = 5.8 Hz, NH), 4.59 (s, 2 H, $HONCH_2Ar$), 4.36 (d, 2 H, J = 5.8 Hz, $ArCH_2NH$), 2.96 (s, 3 H, SO_2CH_3), 1.29 (s, 9 H, $C(CH_3)_3$).

<318> 실시예 49. N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[4-(메틸술포닐아미노)벤질]티오우레아 화합물(61) 제조

<319> N-[4-(메틸술포닐아미노)벤질]히드록실아민 화합물(49) 165mg(0.5mmol)과 디이소프로필에틸아민 0.13㎖(0.75 mmol)를 DMF 3 ㎖에 넣고 1시간동안 실온에서 저어주었으며, 혼합물은 상기의 화합물 26(0.5 mmol)을 넣어주고 실온에서 20시간동안 저어주었다. 반응 혼합물은 물로 희석하였으며, 수회동안 에틸아세테이트로 추출한 후, 유기층은 물로 세척하고 황산마그네슘으로 건조하며, 감압농축하였다. 잔사물은 컬럼 크로마토그래피(전개용매:에틸아세테이트/헥산=2:1)로 분리 및 정제하여 흰색 고체인 N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[4-(메틸술포닐아미노)벤질]티오우레아 화합물(61) (수율 35%)를 수득하였다(표 6 참조).

<320> 녹는점 : 49 ℃

<321> ^{1}H-NMR($CDCl_3$) δ: 7.37 (d, 2 H, J = 7.6 Hz), 7.14 (d, 2 H, J = 7.6 Hz), 6.88-7.1 (m, 3 H, Ph and NH), 6.6-6.7 (bs, 2 H, NH), 5.24 (m, 2 H, $HONHCH_2Ar$), 4.12 (m, 1 H, CH_2OCO), 3.86 (m, 1 H, CH_2OCO), 3.73 (m, 1 H, CH_2NH), 3.50 (m, 1 H, CH_2NH), 2.97 (s, 3 H, SO_2CH_3), 2.6-2.75 (m, 2 H, $CHCH_2Ar$), 2.38 (m, 1 H, $CHCH_2Ar$), 2.21-2.23 (d, 6 H, 2 x CH_3), 1.23 (s, 9 H, $C(CH_3)_3$).

<322> IR (KBr): 3244, 1715, 1514, 1457, 1398, 1329, 1286, 1154 cm^{-1}

<323> Mass *m/z* : 536 (MH^+)

<324> 실시예 50. N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[3-플로로-4-(메틸술포닐아미노)벤질]티오우레아 화합물(64) 제조

<325> N-[3-플루오로-4-(메틸술포닐아미노)벤질]히드록실아민 화합물(56) 165㎎

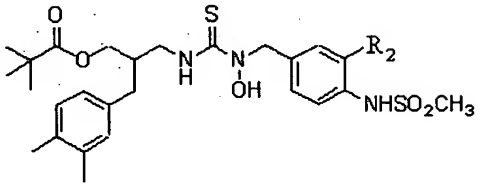
<326> (0.5mmol)과 디이소프로필에틸아민 0.13㎖(0.75 mmol)를 DMF 3 ㎖에 넣고 1시간동안 실온에서 저어주었으며, 혼합물은 상기의 화합물 26(0.5 mmol)을 넣어주고 실온에서 20시간동안 저어주었다. 반응 혼합물은 물로 희석하였으며, 수회동안 에틸아세테이트로 추출한 후, 유기층은 물로 세척하고 황산마그네슘으로 건조하며, 감압농축하였다. 잔사물은 컬럼 크로마토그래피(전개용매:에틸아세테이트/헥산=2:1)로 분리 및 정제하여 무색의 오일인 N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[3-플로로-4-(메틸술포닐아미노)벤질]티오우레아 화합물(64) (수율 41%)을 수득하였다(표 6 참조).

<327> ^{1}H-NMR($CDCl_3$) δ: 7.45 (t, 1 H, J = 8.25 Hz), 7.31 (m, 1 H), 7.12-7.25 (m, 2 H), 6.9-7.05 (m, 2 H), 6.70 (bs, 1 H, NH), 5.20 (m, 2 H, CH_2NOH), 4.12 (m, 1 H, CH_2OCO),

3.86 (m, 1 H, CH_2OCO), 3.75 (m, 1 H, CH_2NH), 3.48 (m, 1 H, CH_2NH), 3.00 (s, 3 H, SO_2CH_3), 2.6-2.8 (m, 2 H, CH_2Ar), 2.36 (m, 1 H, CH), 2.2-2.3 (m, 6 H, 2 x CH_3), 1.23 (s, 9 H, $C(CH_3)_3$), 1.22 (s, 9 H, $C(CH_3)_3$)

<328> MS *m/z* : 554 (MH^+)

<329> 【화학식 15】



(X I)

<330> 【표 6】

화합물군	화합물	R_2	수율(%)	스펙트럼 데이터
V	61	H	74	^{1}H NMR ($CDCl_3$) δ 7.32 (d, 2 H, *J* = 8.3 Hz), 7.27 (d, 2 H, *J* = 8.3 Hz), 7.18 (d, 2 H, *J* = 8.3 Hz), 7.10 (d, 2 H, *J* = 8.3 Hz), 6.76 (bs, 1 H, NH), 6.69 (bs, 1 H, OH), 6.29 (t, 1 H, *J* = 5.8 Hz, NH), 4.59 (s, 2 H, $HONCH_2Ar$), 4.36 (d, 2 H, *J* = 5.8 Hz, $ArCH_2NH$), 2.96 (s, 3 H, SO_2CH_3), 1.29 (s, 9 H, $C(CH_3)_3$).
	64	F	41	^{1}H-NMR($CDCl_3$) δ : 7.45 (t, 1 H, *J* = 8.25 Hz), 7.31 (m, 1 H), 7.12-7.25 (m, 2 H), 6.9-7.05 (m, 2 H), 6.70 (bs, 1 H, NH), 5.20 (m, 2 H, CH_2NOH), 4.12 (m, 1 H, CH_2OCO), 3.86 (m, 1 H, CH_2OCO), 3.75 (m, 1 H, CH_2NH), 3.48 (m, 1 H, CH_2NH), 3.00 (s, 3 H, SO_2CH_3), 2.6-2.8 (m, 2 H, CH_2Ar), 2.36 (m, 1 H, CH), 2.2-2.3 (m, 6 H, 2 x CH_3), 1.23 (s, 9 H, $C(CH_3)_3$), 1.22 (s, 9 H, $C(CH_3)_3$)

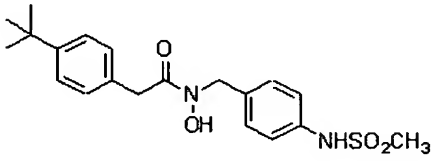
<331> 실시예 51. N-히드록시-N-[4-(메틸술포닐아미노)벤질]-2-(4-*tert*-부틸페닐)아세트아미드 화합물(63) 제조

<332> N-[4-(메틸술포닐아미노)벤질]히드록실아민 화합물(49) 165mg(0.5mmol)과 디이소프로필에틸아민 0.13㎖(0.75 mmol)를 DMF 3 ㎖에 넣고 1시간동안 실온에서 저어주었으며, 혼합물은 상기의 화합물 59(0.5 mmol)를 넣어주고 실온에서 20시간동안 저어주었다. 반응 혼합물은 물로 희석하였으며, 수회동안 에틸아세테이트로 추출한 후, 유기층은 물로 세척하고 황산마그네슘으로 건조하며, 감압농축하였다. 잔사물은 컬럼 크로마토그래피(전개용매:에틸아세테이트/헥산=2:1)로 분리 및 정제하여 흰색 고체인 N-히드록시-N-[4-(메틸술포닐아미노)벤질]-2-(4-*tert*-부틸페닐)아세트아미드 화합물(63)(수율 38%)을 수득하였다(표 7 참조).

<333> ^{1}H-NMR(acetone-d_6) δ 7.32 (d, 2 H, J = 8.3 Hz), 7.25 (s, 4 H), 7.21 (d, 2 H, J = 8.3 Hz), 4.76 (s, 2 H, $HONCH_2Ar$), 3.80 (s, 2 H, $ArCH_2CO$), 2.96 (s, 3 H, SO_2CH_3), 1.28 (s, 9 H, $C(CH_3)_3$).

<334> MS m/z : 391 (MH^+)

<335> 【화학식 16】



<336>

【표 7】

화합물군	화합물	수율(%)	스펙트럼 데이터
VI	63	38	^{1}H NMR (acetone-d_6) δ 7.32 (d, 2 H, J = 8.3 Hz), 7.25 (s, 4 H), 7.21 (d, 2 H, J = 8.3 Hz), 4.76 (s, 2 H, $HONCH_2Ar$), 3.80 (s, 2 H, $ArCH_2CO$), 2.96 (s, 3 H, SO_2CH_3), 1.28 (s, 9 H, $C(CH_3)_3$).

<337> 참조예 1. 바닐로이드 수용체 친화력(binding affinity) 측정 실험

<338> 상기의 실시예 1 내지 51에서 제조된 화합물의 생물학적 효능을 검색하기 위하여 바닐로이드 수용체-1(vanilloid receptor-1, VR-1)에 대한 친화력을 측정하였다.

<339> 1) 세포배양

<340> VR1의 cDNA (pUHG102 VR1 plasmid)가 감염되어 테트라사이클린의 투여 여부에 따라 VR1의 발현을 조절할 수 있는 중국 햄스터 난소(Chinese Hamster Ovary, CHO, ATCC; 미국 세포주 은행 No. CCL-61) 세포로서, 배지에서 테트라사이클린을 제거하면 VR1의 발현이 유도되어지는 테트라사이클린 온/오프 시스템(pTet Off regulatory plasmid, Clontech사, 미국)을 이용하였다. 안정한 세포주를 확립하기 위하여 푸로마이신 10㎍/㎖으로 선택하였으며, 테트라사이클린(시약번호; T-7660, Sigma-Aldrich사, 미국) 1㎍/㎖이 포함되어진 배지에서 유지되어졌다. VR1 결합 시험을 위해서는 48시간 전에 테트라사이클린을 제거한 후 세포배양하였으며, 테트라사이클린이 없는 배지를 사용하여 T75 플라스크에 세포를 깔은 후, 약 90% 밀도가 될 때까지 세포를 배양하였고, 생리식염수(PBS)로 한번 세척한 후, 5mM EDTA를 포함한 생리식염수를 이용하여 세포들을 수집하였으며, 수집된 세포를 가볍게 원심분리하여 침전물을 얻은 후 사용할 때까지 -20 ℃에 보관하였다.

<341> 2) 수용체 친화력 측정 (Competition binding assay)

<342> [3H]레시니페라톡신(RTX)을 이용한 결합 연구는 살라시 등에 의해 발표한 것을 근거로 수행하였다(Szallasi et al.; *Pharmacol. Exp. Ther.*, 262, pp883-888, 1992).

<343> 80pM [3H]RTX, 여러 가지 농도의 경쟁적 결합물질, BSA(Cohn fraction V) 0.25 mg/㎖, $5x10^4$ 내지 $5x10^5$ VR1과 발현 세포를 포함하고 있는 결합시험 혼합물은 최종 부피가 450㎕인 Ca^{2+}와 Mg^{2+}과 BSA 0.25mg/㎖를 포함한 생리식염수에 섞여져 있다. 비특이적 결합 (Non-specific binding)은 100nM의 비방사성 RTX를 함께 섞어 준 후 측정하였으며, 얼음에 꽂아 두었던 반응 혼합물을 37℃에서 60분간 방치하여 반응을 일어나게 하고, 다시 얼음에 꽂음으로써 반응을 종료시켰다. 세포막의 VR1에 결합한 RTX는 원심분리기(12 benchtop centrifuge, Beckman사)를 사용하여 15분간 최고 속도로 원심분리를 하여 막부분을 침전시켜서 결합하지 않은 RTX와 분리시켰으며, 이렇게 분리된 침전물을 포함한 튜브의 끝을 잘라서 신틸레이션 카운터(LS 6500, Beckman-Coulter사, 미국)를 사용하여 방사선 동위원소의 양을 측정하였다. 평형 결합 계수(equilibrium binding parameter)인 평형상수(*Ki*), 최대결합계수(*Bmax*) 및 협력활성(cooperativity) 등은 오리진 6.0(Origin, MicroCal사) 프로그램을 사용하여 힐(Hill) 방정식에 대입하여 결정하였다.

<344> 3) 화합물 샘플제조

<345> 초기 화합물은 디메틸술폭시드(dimethyl sulfoxide, DMSO)에 용해하였으며, 결합 시험을 위해서 Ca^{2+}, Mg^{2+} 및 BSA 0.25mg/㎖를 포함한 생리식염수에 희석하였다.

<346> 실험예 1. 바닐로이드 수용체 칼슘유입 실험

<347> 효현제/길항제로서의 활성을 측정하기 위해 칼슘유입(calcium influx) 실험을 수행하였다.

<348> 특정 분자가 전체 또는 부분 효현제인지를 확인하기 위하여, VR1과 발현하는 CHO세포를 테트라사이클린 온/오프 시스템를 이용하여 $^{45}Ca^{2+}$-흡입량 실험을 수행하였다. 세포를 20 내지 40% 정도의 밀도로 24 웰 플레이트에 깔아서 배양하며, 다음날 VR1의 발현을 유도하기 위하여 테트라사이클린이 제거된 배지로 갈아주고, VR1의 발현 유도 후, 36 내지 40시간 후에 실험을 수행하였다.

<349> $^{45}Ca^{2+}$-흡입량을 측정하기 위해서, 세포를 37℃에서 10분간 총 부피가 500㎕의 1.8mM 염화칼슘을 포함하는 무혈청의 DMEM(Dulbecco's modified Eagles medium, Gibco-BRL, Invitrogen사, 미국) 에서 배양하며, 이 때 배지에 BSA 0.25 mg/㎖, 1 Ci/㎖ ^{45}Ca(5-30 Ci/g을 ICN, ICN biomedicals사, 미국)를 넣어 주고 다양한 농도의 화합물을 첨가하여 주며 그 정도를 측정하였다. 10분 배양 후, 1.8mM 염화칼슘을 포함하는 차가운 생리식염수를 이용하여 3번 세포를 세척하고, 세포 내에 침투하지 않은 남아 있는 ^{45}Ca를 제거하였다. 400㎕ RIPA 완충액(조성 : 50mM 트리스 pH 7.4; 150mM 염화나트륨; 1% 트리톤 X-100; 0.1% SDS; 1% 소듐 데옥시콜레이트)을 각각의 웰에 넣어서 세포를 터뜨린 후 20분간 플레이트를 서서히 흔들어 주었으며, 300㎕의 세포용해물을 각 웰로부터 꺼내어 각각의 바이알에 담은 후, 신틸레이션 카운터를 사용하여 방사선 동위원소의 활성도를 측정하였다. 이 때, 각 실험당 한 농도에 4개의 웰을 사용하여 수행

하였으며, 얻어진 데이터들은 힐 방정식에 대입하여 그 값을 분석하였고, 적어도 한 개의 화합물에 대하여 3번의 실험이 실행되어졌다.

<350> 길항제로서의 활성을 측정하기 위하여, $^{45}Ca^{2+}$-흡입량을 자극하기 위한 혼합물에 50nM의 캡사이신이 더하여졌으며 효현제 활성도 측정과 동일한 방법으로 그 활성을 측정하였다. 만일 특정 화합물이 10μM의 농도까지 더하였을 경우에도 캡사이신에 의하여 유도되어지는 활성을 바꾸지 못하였다면 이 화합물은 전체 효현제로 간주하였으며, 각 화합물의 바닐로이드 수용체 친화력 및 칼슘유입실험 결과를 하기의 표 8에 나타내었다(표 8 참조).

<351> 【표 8】

화합물	화합물 코드	Ki(nM) (VR1/CHO)	EC_{50}(nM) (VR1/CHO)	IC_{50}(nM) (VR1/CHO)
캡사제핀		1350(±50)	NE	520(±12)
28	JYL-1627	1092(±145)	NE	470.2(197.8)
29	MY-594	926(±74)	2008(±198)	NE
30	SU-190	802(±187)	>7062	NE
31	MY-546	1308.3(±209.8)	NE	579(±42.5)
32	MY-570	1328.4(±311.1)	NE	635(±51.8)
33	SU-308	1920.8(±333.7)	12340(±2922)	NE
34	SU-306	2271.6(±731.9)	NE	NE
35	SU-66	1041.8(±72.8)	1233	212.5(±85.3)
36	MY-650	396(±62)	809(±126)	NE
37	SU-154	211.6(±39.6)	NE	93.67(±14)
38	SU-288	623.5(±152.3)	1352(±136)	NE
39	SU-276	220.6(±54.5)	NE	757.4(±65)
40	SU-552	535.6(±89.1)	weak	NE
41	SU-530	404.8(±15.2)	weak	weak
45	JYL-1635	6375.3(±3059)	3504(±1387)	6589(±1986)
60	JYL-1371	4257(±372)	NE	465(±103)
61	LJO-310	481.1(±66.9)	weak	weak
62	JYL-1453	3495(±621)	1055.4(±35.4)	NE
63	JYL-1455	5309(±725)	1963(±402)	NE
64	SU-578	545.8(±52.7)	weak	NE

<352> 실험예 3. 진통효과 실험 (초산-유도 라이팅 테스트)

<353> 본원 제조방법으로 제조된 화합물들의 진통제로서의 효능을 검색하기 위한 진통 효과 실험으로서, 초산 유도 라이팅(acetic acid-induced writhing test) 시험법을 응용하여 시험하였다(Lee, J. W., *Bioorg. Med. Chem.* pp19-31, 2001).

<354> 평균 체중 25g의 웅성 ICR 마우스(CD-1; Biogenomics사, 한국)를 12시간 명암주기로 조절된 환경(명주기는 오전 6시에서 오후 6시로 설정)에서 물과 먹이를 자유롭게 먹을 수 있도록 사육해 실험에 이용하였으며, 온도와 습도는 각각 22±2℃와 50±5%를 유지하였다.

<355> 마우스는 실험 시작하기 30분전에 실험방에 미리 두어 환경에 적응하도록 하였으며, 그 후 마우스는 화학적 자극제인 초산을 1.2% 생리식염수에 조제해 개체당 0.3㎖를 복강주사로 투여하고, 투명한 아크릴 상자(15x15x15 cm)에 넣은 5분 후부터 20분간 뒤틀림 반응(abnormal stretching)의 횟수를 측정하였다. 동물은 한 농도당 10마리를 사용하였으며, 약물은 1:1:8의 비를 갖는 에탄올/트윈-80/생리식염수 혹은 1:1:8의 비를 갖는 크레모포(cremophor) EL/DMSO/증류수(10/10/80)의 혼합 용매에 녹여 초산투여 30분전에 0.2㎖ 복강 투여하였다. 각각의 약물들의 효과는 4 내지 7개의 각각 다른 농도에서 실험하였으며, 용해용 용매만 투여한 대조군에서의 동물의 평균 뒤틀림 횟수를 35로 하여 기준으로 삼았고, 약물 투여군에서의 뒤틀림 횟수의 감소를 진통효과의 지표로 활용하였다. 진통효과의 지표(eff)는 하기의 수학식 1과 같이 정의하였다.

<356> 【수학식 1】 진통효과(eff) = 100 -((약물투여군의 뒤틀림 횟수/대조군의 뒤틀림 횟수) x 100)

<357> 각각의 약물에 대한 진통효과 결과는 ED_{50}값으로 나타내었으며, ED_{50}값은 약물의 농도 반응 그래프를 이용하여 용해용 용매만 투여한 대조군의 뒤틀림 횟수와 비교하여 50% 감소를 나타내는 값에서의 농도로 정의하였으며, 각 화합물의 진통효과를 하기의 표 9에 나타내었다.

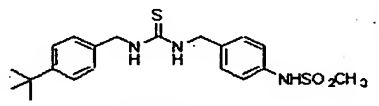
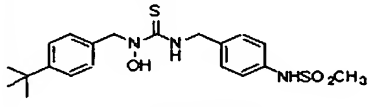
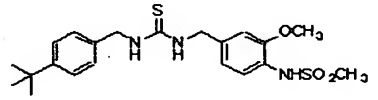
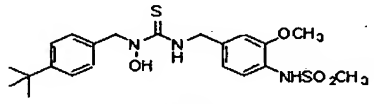
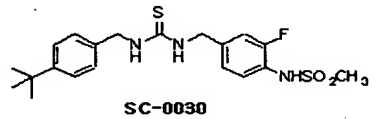
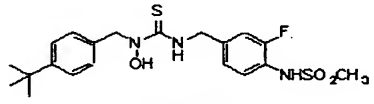
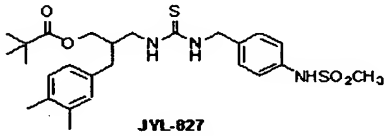
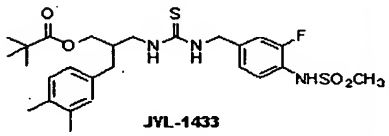
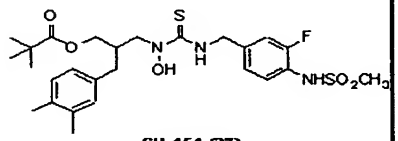
<358> 【표 9】

티오우레아	ED_{50}(μg/kg)	N-하이드록시 티오우레아	ED_{50}(μg/kg)
KJM-429	1,410 (±320)	28(JYL-1627)	1,560(±270)
JYL-511	0.022(±0.118)	29(MY-594)	0.103(±0.061)
SC-0030	1.257(±0.0074)	30(SU-190)	1.072(±0.151)
JYL-827	2,620(±2,380)	35(SU-66)	2,600(±1,100)
JYL-1433	7.429(±8.4)	37(SU-154)	0.065(±0.056)
<참고> 케토롤락(Ketorolac) ED_{50} (μg/kg) = 2820			

<359> 실험 결과, 선행특허인 한국특허출원 제 2001-50093의 티오우레아계 화합물인 JYL-827, JYL-1433과 비교할 때, 나머지 부분은 그대로 유지하고 티오우레아기 대신 N-히드록시티오우레아로 변환한 화합물인 35 (SU-66), 37 (SU-154)가 상대적으로 더욱 우수한 진통 효과를 나타내고 있는데, 즉, 37 (SU-154) > JYL-1433, 35 (SU-66) > JYL-827 (표 10 참조)의 결과를 나타내었으며, 특히 화합물 37 (SU-154)의 경우 지금까지의 알려진 진통제 중 가장 강력한 진통효과를 보이는 화합물 중 하나로 현재 수술 후 환자 진통제로 사용되고 있는 케토롤락 (Ketorolac)에 비해 43,000배 수준에 달하는 것으로 계산되었다(표 10 및 도 1 참조).

<360>

【표 10】

티오우레아	N-히드록시 티오우레아
 KJM-429	 JYL-1627 (28)
 JYL-1511	 MY-594 (29)
 SC-0030	 SU-190 (30)
 JYL-827	 SU-66 (35)
 JYL-1433	 SU-154 (37)

<361> 결과적으로, 본원에서 제조한 바닐로이드 수용체-1(VR-1)에 대한 길항제로서 신규한 N-하이드록시 티오우레아, 우레아 및 아미드계 유도체 화합물이 통증 및 염증성 질환 등에 효과적으로 사용될 수 있음을 확인할 수 있었다.

<362> 실험예 4. 독성 실험

<363> 본원에서 제조된 화합물들의 독성을 시험하기 위하여, 동물실험을 수행하였다.

<364> 25±5g의 ICR계 마우스(중앙실험동물)와 235±10g의 특정병원부재(SPF) 스프라그-도올리(Sprague Dawley, Biogenomics사) 래트를 각각 3마리씩 3군으로 나누어 본 발명의 화합물 35 및 37을 각각 20mg/kg, 10mg/kg, 1mg/kg의 용량으로 복강투여한 후 24시간 동안 독성여부를 관찰하였다.

<365> 실험 결과, 3군 모두에서 사망한 예를 전혀 관찰할 수 없었고, 체중 증가, 사료 섭취량 등에서 외견상 대조군과 별다른 증상을 찾아볼 수 없었다. 따라서 N-하이드록시 티오우레아, 우레아 및 아미드계 유도체 화합물의 경우 안전한 약물임을 확인할 수 있었다.

<366> 본 발명의 N-하이드록시 티오우레아, 우레아 및 아미드계 유도체 화합물은 아래와 같은 제형으로 투여할 수 있으며, 아래의 제제 실시예는 본 발명을 예시하는 것일 뿐, 이에 의해 본 발명의 내용이 제한되는 것은 아니다.

<367> 제제예 1. 산제의 제조

<368> 화합물 35의 건조분말 500mg

<369> 옥수수전분 100mg

<370> 유 당 100mg

<371> 탈 크 10mg

<372> 상기의 성분들을 혼합하고 기밀 포에 충진하여 산제를 제조한다.

<373> 제제예 2. 정제의 제조

<374> 화합물 37의 건조분말 100mg

<375> 옥수수전분 100mg

<376> 유 당 100mg

<377> 스테아린산 마그네슘 2mg

<378> 상기의 성분들을 혼합한 후 통상의 정제의 제조방법에 따라서 타정하여 정제를 제조한다.

<379> 제제예 3. 캡슐제의 제조

<380> 화합물 35의 건조분말 50mg

<381> 유 당 50mg

<382> 스테아린산 마그네슘 1mg

<383> 상기의 성분들을 혼합한 후 통상의 캡슐제의 제조방법에 따라서 타정하여 젤라틴 캡슐에 충진하여 제조한다.

<384> 제제예 4. 주사제의 제조

<385> 화합물 37의 건조분말 10mg

<386> 주사용 멸균 증류수 적량

<387> pH 조절제 적량

<388> 통상의 주사제의 제조방법에 따라서 활성성분을 주사용 증류수에 용해하고 pH를 약 7.5로 조절한 다음 전체를 주사용 증류수로 2㎖ 용량의 앰플에 충진하여 멸균시켜서 주사제를 제조한다.

<389> 제제예 5. 액제의 제조

<390> 화합물 35의 건조분말 1g

<391> 이성화 당 10g

<392> 서 당 10g

<393> 레몬향 적량

<394> 정제수 적량

<395> 통상의 액제의 제조방법에 따라서 정제수에 각각의 성분을 가하고 용해시키고 레몬향을 적량 가한 다음 정제수를 가하여 전체를 100㎖로 조절한 후 갈색병에 충진하여 멸균시켜서 액제를 제조한다.

<396> 상기 조성비는 비교적 기호음료에 적합한 성분을 바람직한 실시예로 혼합 조성하였지만, 수요계층, 수요국가, 사용 용도 등 지역적, 민족적 기호도에 따라서 그 배합비를 변형 실시하여도 무방하다.

【발명의 효과】

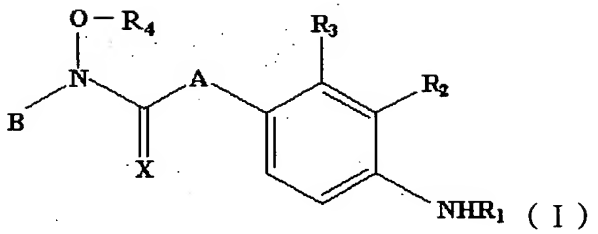
<397> 본 발명의 신규한 N-하이드록시 티오우레아, 우레아 및 아미드계 (N-hydroxy thiourea, urea and amide) 유도체 화합물 및 이를 함유하는 약학조성물은 바닐로이드 수용체 -1(Vanilloid Receptor-1; VR1)에 대한 길항제로서 작용할 뿐만 아니라, 진통활성이 탁월하여 통증, 급성 통증, 만성 통증, 신경병적 통증, 수술후 통증, 편두통, 관절통, 신경병증, 신경손상, 당뇨병성 신경병, 신경변성 질환, 신경성 피부질환, 뇌졸중, 방광과민증, 과민성

장증후군, 천식과 만성폐색성 폐질환 등 호흡기 이상, 피부, 눈, 점막의 자극, 위-십이지장 궤양, 염증성 장 질환 및 염증성 질환 등의 예방 및 치료에 효과적인 무독성 진통제로 유용하게 사용될 수 있다.

【특허청구범위】

【청구항 1】

하기 일반식 (I) 로 표기되는 화합물 또는 이들의 약제학적으로 허용 가능한 염 또는 이성질체:

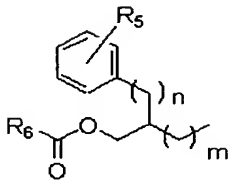


(I)

상기의 식에서,

X 는 황원자 또는 산소원자이며;

A는 아미노메틸렌기 또는 메틸렌기이며,

B 는 4-*tert*-부틸벤질, 3,4-디메틸페닐프로필, 올레일기 또는  (I -1) (식 중 m은 0 또는 1, n은 1 또는 2)이고,

R_1은 할로겐으로 치환 또는 비치환된 탄소수 1 내지 5의 저급알킬설폰, 아릴설폰 또는 탄소수 1 내지 5의 저급알킬카보닐기이며;

R_2은 수소원자, 메톡시기 또는 할로겐기이며;

R_3는 수소원자, 메톡시기 또는 할로겐기이며;

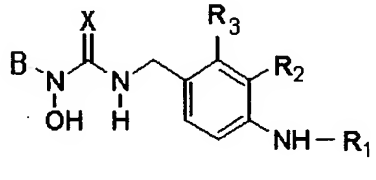
R_4는 수소원자 또는 탄소수 1 내지 5의 알킬기이며;

R_5는 수소원자, 탄소수 1 내지 5의 저급알킬기이며;

R_6는 탄소수 1 내지 5의 저급알킬기 또는 페닐기이다.

【청구항 2】

제 1항에 있어서, A가 아미노메틸렌기인 일반식 (Ⅲ)으로 표기되는 화합물 또는 그의 이성질체.



(Ⅲ)

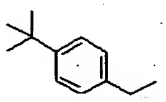
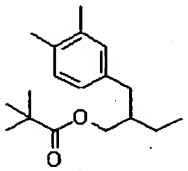
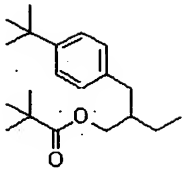
상기의 식에서,

X 는 황원자 또는 산소원자이며;

R_1은 할로겐으로 치환 또는 비치환된 탄소수 1 내지 5의 저급알킬설폰, 아릴설폰 또는 탄소수 1 내지 5의 저급알킬카보닐기이며;

R_2은 수소원자, 메톡시기 또는 할로겐기이며;

R_3는 수소원자, 메톡시기 또는 할로겐기이며;

B는  ,  ,  기이다.

【청구항 3】

제 2항에 있어서,

N-(4- *tert*-부틸벤질)-N-히드록시-N-[4-(메틸술포닐아미노)벤질]티오우레아,

N-(4-*tert*-부틸벤질)-N-히드록시-N-[3-메톡시-4-(메틸술포닐아미노)벤질]티오우레아,

N-(4- *tert*-부틸벤질)-N-히드록시-N-[3-플루오로-4-(메틸술포닐아미노)벤질]티오우레아,

N-(4-*tert*-부틸벤질)-N-히드록시-N-[3-클로로-4-(메틸술포닐아미노)벤질]티오우레아,

N-(4- *tert*-부틸벤질)-N-히드록시-N-[4-(메틸술포닐아미노)-3-니트로벤질]티오우레아,

N-(4-*tert*-부틸벤질)-N-히드록시-N-[2-플루오로-4-(메틸술포닐아미노)벤질]티오우레아,

N-(4- *tert*-부틸벤질)-N-히드록시-N-[2-클로로-4-(메틸술포닐아미노)벤질]티오우레아,

N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[4-(메틸술포닐아미노)벤질]티오우레아,

N-[2-(3,4- 디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[3-메톡시-4-(메틸술포닐아미노)벤질]티오우레아,

N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[3-플루오로-4-(메틸술포닐아미노)벤질]티오우레아,

N-[2-(3,4- 디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[2-플루오로-4-(메틸술포닐아미노)벤질]티오우레아,

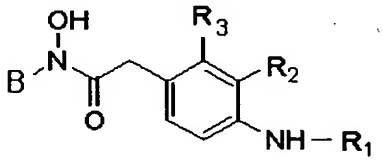
N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[2-클로로-4-(메틸술포닐아미노)벤질]티오우레아,

N-[2-(4- *tert*-부틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[4-(메틸술포닐아미노)벤질]티오우레아,

N-[2-(4-*tert*-부틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[3-플루오로-4-(메틸술포닐아미노)벤질]티오우레아로 구성된 군으로부터 선택된 화합물.

【청구항 4】

제 1항에 있어서, X는 산소원자이고, A는 메틸렌기인 하기 일반식 (IV)로 표기되는 화합물 또는 그의 이성질체.



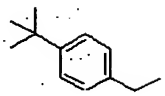
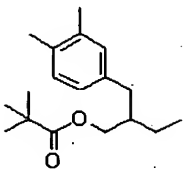
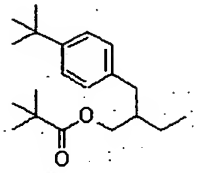
(IV)

상기의 식에서,

R_1은 할로겐으로 치환 또는 비치환된 탄소수 1 내지 5의 저급알킬설폰, 아릴설폰 또는 탄소수 1 내지 5의 저급알킬카보닐기이며;

R_2은 수소원자, 메톡시기 또는 할로겐기이며;

R_3는 수소원자, 메톡시기 또는 할로겐기이며;

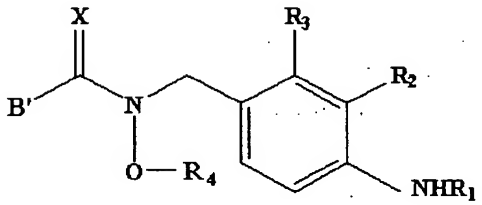
B는  ,  ,  기이다.

【청구항 5】

제 4항에 있어서, N-(4-*tert*-부틸벤질)-N-히드록시-[4-(메틸술포닐아미노)페닐]아세트아미드인 화합물.

【청구항 6】

하기 일반식 (Ⅱ) 로 표기되는 화합물 또는 이들의 약제학적으로 허용 가능한 염 또는 이성질체:

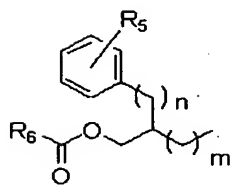


(Ⅱ)

상기의 식에서,

X 는 황원자 또는 산소원자이며;

B'는 B 또는 B로 치환된 2급 아민기이며,



(Ⅱ-1) (

B 는 4-*tert*-부틸벤질, 3,4-디메틸페닐프로필, 올레일기 또는

식 중 m은 0 또는 1, n은 1 또는 2)이고,

R_1은 할로겐으로 치환 또는 비치환된 탄소수 1 내지 5의 저급알킬설폰, 아릴설폰 또는 탄소수 1 내지 5의 저급알킬카보닐기이며;

R_2은 수소원자, 메톡시기 또는 할로겐기이며;

R_3는 수소원자, 메톡시기 또는 할로겐기이며;

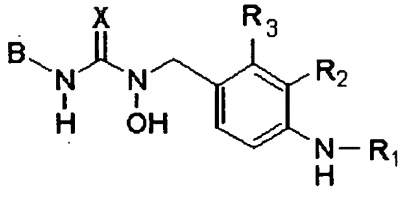
R_4는 수소원자 또는 탄소수 1 내지 5의 알킬기이며;

R_5는 수소원자, 탄소수 1 내지 5의 저급알킬기이며;

R_6는 탄소수 1 내지 5의 저급알킬기 또는 페닐기이다.

【청구항 7】

제 6항에 있어서, B'는 B로 치환된 2급 아민기인 하기 일반식 (Ⅴ)으로 표기되는 화합물 또는 그의 이성질체.



(Ⅴ)

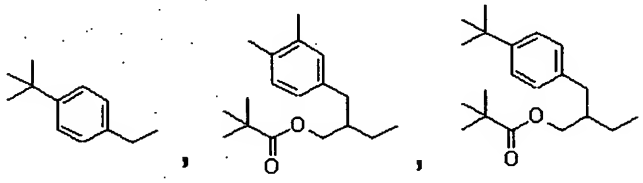
상기의 식에서,

X는 황원자 또는 산소원자이며;

R_1은 할로겐으로 치환 또는 비치환된 탄소수 1 내지 5의 저급알킬설폰, 아릴설폰 또는 탄소수 1 내지 5의 저급알킬카보닐기이며;

R_2은 수소원자, 메톡시기 또는 할로겐기이며;

R_3는 수소원자, 메톡시기 또는 할로겐기이며;

B는  기이다.

【청구항 8】

제 7항에 있어서,

N-(4- *tert*-부틸벤질)-N-히드록시-N-[4-(메틸술포닐아미노)벤질]티오우레아,

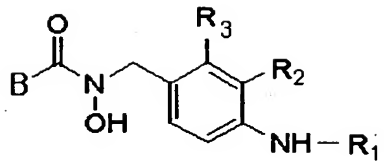
N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[4-(메틸술포닐아미노)벤질]티오우레아,

N-(4- *tert*-부틸벤질)-N-히드록시-N-[4-(메틸술포닐아미노)벤질]우레아,

N-[2-(3,4-디메틸벤질)-3-(피발로일옥시)프로필]-N-히드록시-N-[3-플루오로-4-(메틸술포닐아미노)벤질]티오우레아로 구성된 군으로부터 선택된 화합물.

【청구항 9】

제 6항에 있어서, B'는 B인 하기 일반식 (VI)으로 표기되는 화합물 또는 그의 이성질체.



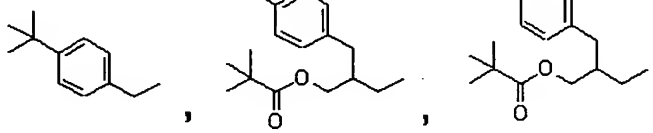
(VI)

상기의 식에서,

R_1은 할로겐으로 치환 또는 비치환된 탄소수 1 내지 5의 저급알킬설폰, 아릴설폰 또는 탄소수 1 내지 5의 저급알킬카보닐기이며;

R_2은 수소원자, 메톡시기 또는 할로겐기이며;

R_3는 수소원자, 메톡시기 또는 할로겐기이며;

B는  기이다.

【청구항 10】

제 9항에 있어서, N-히드록시-N-[4-(메틸술포닐아미노)벤질]-2-(4-*tert*-부틸페닐)아세트아미드인 화합물.

【청구항 11】

제 1항의 일반식 (Ⅰ) 화합물을 유효 활성 성분으로 하고 약학적으로 허용되는 담체를 포함하는 바닐로이드 수용체에 대한 길항 활성을 갖는 약학 조성물.

【청구항 12】

제 6항의 일반식 (Ⅱ) 화합물을 유효 활성 성분으로 하고 약학적으로 허용되는 담체를 포함하는 바닐로이드 수용체에 대한 길항 활성을 갖는 약학 조성물.

【청구항 13】

제 11항 또는 제 12항에 있어서, 바닐로이드 수용체의 길항 활성에 의한 통증, 급성 통증, 만성 통증, 신경병적 통증, 수술후 통증, 편두통, 관절통, 신경병증, 신경손상, 당뇨병성 신경병, 신경변성 질환, 신경성 피부질환, 뇌졸중, 방광과민증, 과민성 장증후군, 천식과 만성 폐색성 폐질환 등 호흡기 이상, 피부, 눈, 점막의 자극, 발열, 위-십이지장궤양, 염증성 장 질환 또는 이들 염증성 질환 및 급박성 요실금 질환의 예방 및 치료에 효과적인 약학조성물.

【청구항 14】

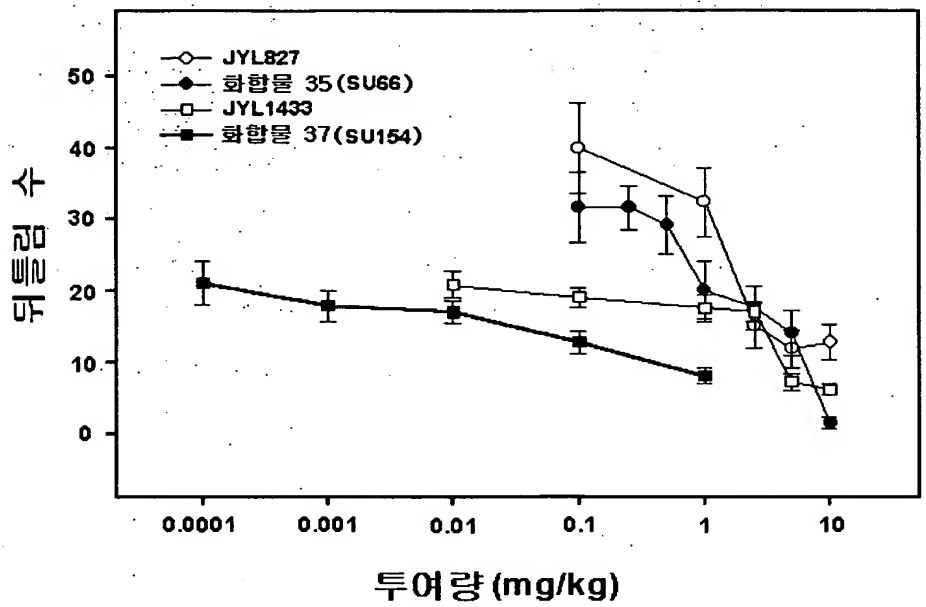
제 1항 내지 10항 중 어느 한 항의 화합물을 유효성분으로 하고, 약학적으로 허용되는 담체를 포함하는 소염 및 진통의 예방 및 치료용 조성물.

【청구항 15】

제 1항 내지 제 10항 중 어느 한 항의 화합물을 유효성분으로 하고, 약학적으로 허용되는 담체를 포함하는 급박성 요실금 질환의 예방 및 치료용 조성물.

【도면】

【도 1】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화합물 35(SU66)
JYL1433
화합물 37(SU154)
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10
투여량(mg/kg)